Zohydro™ ER

Hydrocodone Bitartrate

Extended-Release Capsules

Anesthetic and Analgesic Drug Products Advisory Committee

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LIST OF ABBREVIATIONS

Acronym/Abbreviation	Definition
AE	Adverse event
ANCOVA	Analysis of covariance
APAP	Acetaminophen
ASI-MV	Addiction Severity Index – Multimedia Version
BMI	Body mass index
BPI	Brief Pain Intensity
CDER	Center for Drug Evaluation and Research
CE	Continuing education
CHAT	Comprehensive Health Assessment for Teens
CI	Confidence intervals
CLBP	Chronic lower back pain
CNS	Central nervous system
COMM	Current Opioid Misuse Measure
COWS	Clinical Opioid Withdrawal Scale
CYP450	cytochrome P450
DEA	Drug Enforcement Administration
EERW	Enriched enrollment with randomized withdrawal
Embeda®	Morphine/naltrexone extended-release
ETASU	Elements to assure safe use
ER	Extended-release
EXALGO®	Hydromorphone extended-release
FDA	Food and Drug Administration
GI	Gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HC-ER	Hydrocodone bitartrate extended-release capsules (Zohydro ER)
HRQL	Health related quality of life
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IND	Investigational New Drug
IR	Immediate release
ITT	Intent-to-Treat
Kadian®	Morphine sulfate extended-release
LA	Long acting
MAP-PC	Managing Addiction and Pain in Primary Care
MDD	Major depression disorder
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	New Drug Application
NIDA	National Institutes of Drug Abuse
NIH	National Institute of Health
NRS	Numerical rating scale

NSAIDs	Non-steroidal anti-inflammatory drugs
Nucynta® ER	Tapentadol
OA	Osteoarthritis
ODI	Oswestry Disability Inventory
Opana® ER	Hydromorphone extended-release
Palladone®	Hydromorphone extended-release
PK	Pharmacokinetic
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SES	Standardized effect size
SGAM	Subject global assessment of medication
SOAPP®	Screener and Opioid Assessment for Patients with Pain
SODAS®	Spheroidal Oral Drug Absorption System
SOWS	Subject Opioid Withdrawal Scale
SR	Sustained release
TDD	Total daily dose
TEAE	Treatment-emergent adverse event
TEDS	Treatment Episode Data Set
US	United States
WIS	Web Informed Services
Zohydro ER	Hydrocodone bitartrate extended-release capsules (HC-ER)

1 EXECUTIVE SUMMARY

Zogenix, Inc. is seeking United States (US) Food and Drug Administration (FDA) approval for hydrocodone bitartrate extended-release capsules CII (HC-ER, proposed trade name Zohydro ER), for the management of moderate-to-severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time. The analgesic efficacy and safety of hydrocodone is well known through decades of clinical use of combination products for the treatment of pain, but it has never been available in the US as a single-agent product. To support treatment of people suffering from chronic moderate to severe pain, while reducing the risk of liver injury and where higher doses of hydrocodone is the optimal treatment option for those patients, Zohydro ER was developed without acetaminophen (APAP) in an extended release (ER) formulation that enables twice daily (q12h) administration.

Hydrocodone /APAP is the most prescribed opioid analgesic yet is the only opioid within the class that is regulated as Schedule III (all others are Schedule II). The absence of a single-entity ER hydrocodone limits its utility clinically and prevents it from being monitored under a standard REMS like all other ER or long acting (LA) opioids. Zohydro ER, which would be classified as Schedule II, would bring hydrocodone under important regulatory uniformity and controls. It also provides an opportunity to re-educate and inform prescribers about the attributes of hydrocodone which has been left behind in the safe use and other REMS efforts to date.

Despite the availability of other ER opioid analgesic products, there remains a significant need for additional safe and effective ER opioid analgesic products for patients with chronic pain. Responsiveness to opioids varies greatly between individual pain patients. Comparative effectiveness, tolerance and cross-tolerance between opioids also vary greatly within individual patients. Over the course of chronic pain therapy, the prescriber needs the flexibility to use the same opioid when converting their patient from an IR treatment to their first ER regimen. Prescribers also need more choices when it is necessary to rotate to another ER opioid when issues of effectiveness, tolerance or tolerability develop on a current ER opioid analgesic regimen.

Zogenix has completed a development program that was agreed to with FDA and that includes non-clinical, pharmacology and clinical studies for Zohydro ER, and has submitted its New Drug Application (NDA). The results of the studies show Zohydro ER to be safe and effective for the intended use. Recognizing the wide-scale public health issue associated with abuse, misuse and diversion of opioids, Zogenix is committed to the safe use of HC-ER. This briefing document describes both the FDA-required Risk Evaluation and Mitigation Strategy (REMS) for any ER or LA opioid, as well as additional voluntary risk mitigation programs that Zogenix has committed to, including a targeted and conservative plan to introduce Zohydro ER into the marketplace. Safe use efforts introduced by Zogenix will specifically and proactively address the primary risks of misuse, abuse, diversion, inappropriate prescribing, and unintentional overdose of HC-ER, and will ensure that the important benefits seen in patients with chronic pain outweigh the risks.

1.1 Chronic Pain: Burden of Disease and Medical Need

Chronic pain is defined as "pain that persists beyond an expected time frame for healing." Chronic low back pain (CLBP) is the most common cause of disability in industrialized nations. Other common types of chronic non-cancer pain include arthritis pain, headache, neuropathic pain, and fibromyalgia. It is estimated that there are approximately 100 million adults in the US affected by chronic pain (Institute of Medicine, 2011) and many people with moderate to severe chronic pain have yet to find adequate relief. Several studies have also highlighted the increasing prevalence of chronic pain over time (Manchikanti 2012a; Freburger 2009; Harkness 2005).

The efficacy of opioids for chronic pain treatment is established across a wide spectrum of chronic pain conditions. The most recently published guidelines in 2012 by the American Society of Interventional Pain Physicians (ASIPP) focused on the objective of providing physicians concise guidance to improving patient access to opioids and to avoid diversion and abuse (Manchikanti 2012b). Both immediate-release (IR) and ER formulations of opioids are marketed in the US. Except for hydrocodone, all orally administered opioids exist in both IR and ER formulations. Furthermore, hydrocodone is only available in a combination tablet form with a non-opioid analgesic; the most frequently prescribed being HC/APAP (136 million prescriptions in 2011).

A subgroup of patients on IR hydrocodone for chronic pain will eventually meet clinical criteria for the addition of an ER product; these are typically patients with pain around-the-clock, who have significant pain interference with sleep, awaken with pain, may have peak-dose side effects, and may need to take medication every few hours. Physicians are generally trained to use the same molecule when adding an ER opioid to an IR regimen, in order to take advantage of the idiosyncratic efficacy and tolerability often seen with opioids. In such patients on IR hydrocodone, there has been no ER option, necessitating using ER formulations of other molecules. A significant proportion of patients on hydrocodone-acetaminophen have either frank liver disease or risk factors; for this subset, the availability of a non-acetaminophen formulation is an important therapeutic option. APAP overdose is a leading cause of acute liver failure in the US, with 63% of the unintentional overdoses attributed to the use of HC/APAP combination products (Mincha 2010).

Zohydro ER will also fulfill a role in opioid rotation, a practice needed to treat some patients with chronic pain. Current clinical guidelines support opioid rotation (changing from one opioid to another opioid) in patients on chronic opioid therapy who are unable to maintain therapeutic goals with their current opioid (Chou 2009). The pharmacological basis of opioid rotation is related to incomplete cross-tolerance to the analgesic and non-analgesic responses between opioids, which could potentially result in a better balance of analgesic and side effects when one opioid is changed for another (Slatkin 2009). While well-controlled studies are lacking, opioid rotation is considered a necessary clinical practice in the management of chronic pain (Fine 2009; Slatkin 2009; Nalamachu 2011), and up to 30% of patients will require opioid rotation at some time (Slatkin 2009). HC-ER would provide an additional therapeutic option for rotation to clinicians treating patients with chronic pain with extended release opioids.

In summary, although there are several choices for extended-release opioids, the availability of another option only increases the tools in the physician's armamentarium against chronic pain.

1.2 Overview of HC-ER Development Program

The development of HC-ER was initiated by Elan Corporation (now Alkermes) in 2002. Zogenix acquired the US rights to HC-ER from Elan in November 2007. Zogenix held an End-of-Phase 2 meeting with FDA in May 2008 where agreement was reached on nonclinical, clinical, and CMC elements for further development. It was agreed that a single well-controlled efficacy study in chronic low back pain would be sufficient to establish efficacy in the intended patient population, and that the safety database of HC-ER would need to include exposures to HC-ER in at least 300 subjects for 6 months, and at least 100 subjects for one year. Following completion of the Phase 3 clinical program, Zogenix held pre-NDA meetings with FDA in November 2011, and the NDA for HC-ER was submitted on 01 May 2012. The application is currently under review with an action date of 01 March 2013.

The dosage form for HC-ER is based on the Alkermes Spheroidal Oral Drug Absorption System (SODAS), an oral, multi-particulate formulation technology utilized in several FDA-approved extended-release products including several that are Schedule II. HC-ER is composed of a blend of beads containing hydrocodone with (80%) and without (20%) rate controlling polymers that impact drug release by diffusion in the gastrointestinal tract. The extended release properties of the formulation allow HC-ER to be administered twice-daily (q12h).

1.3 Overview of Clinical Studies

1.1.1 Pharmacology and Biopharmaceutical Studies

A total of eight clinical pharmacology studies (Phase 1 and Phase 2) were conducted to characterize the bioavailability, pharmacokinetics and pharmacodynamics of HC-ER. The single-dose pharmacokinetic profile of HC-ER is characterized by a biphasic absorption profile which supports a 12-hour dosing interval. Compared to the same dose of HC in HC/combination analgesic products, C_{max} is lower for HC-ER and occurs at a later T_{max} (approx. 6 hours). The steady state characteristics of HC-ER demonstrated relatively stable levels of hydrocodone and dose proportional pharmacokinetics. The average plasma concentrations at steady state values were ~20% lower than mean C_{max} values and peak-to-trough fluctuation was relatively low (approximately 50 to 60%). The concomitant use of alcohol and HC-ER was evaluated for dose dumping; there was no significant effect of 20% alcohol on HC-ER pharmacokinetic parameters. Conversely, the rate of absorption of HC from HC-ER was affected by a severe challenge involving co-ingestion with 40% alcohol in the fasted state, as exhibited by an increase in C_{max} and an earlier T_{max}. The magnitude of these effects with 40% alcohol were within the range reported for other marketed ER opioid

products and underscore the importance of class-wide labeling that warns against the use of alcohol with opioid products. There was no food effect on the extent of absorption of HC from HC-ER. Pharmacology studies in special populations indicated no need for initial dose adjustments in patients with hepatic or renal impairment.

1.1.2 Clinical Efficacy and Safety Studies

A total of four Phase 2 and Phase 3 studies were completed. Safety data come from a total of 1,568 study subjects. Efficacy and safety information for the chronic pain indication come from two adequate and well-designed, Zogenix-sponsored Phase 3 studies encompassing 1,143 adult subjects, ZX002-0801 (Study 801) and ZX002-0802 (Study 802).

1.1.1.1 Pivotal Study 801

ZX002-0801 (Study 801) was a multicenter, double-blind, placebo-controlled study that used an enriched enrollment randomized withdrawal design (EERW), agreed between Zogenix and the Agency as an appropriate and validated approach to studying the efficacy of an extended-release opioid. Pivotal studies of most recently approved ER opioid products used this design (e.g. Opana ER, Embeda, Exalgo, and Nucynta ER). An EERW study is different from many placebo-controlled studies, in that enrichment for drug-responsive patients occurs during an open-label run-in period, and then the primary endpoint is loss of pain control when responders are randomized to placebo or active drug. FDA refers to this as predictive enrichment. Subjects were required to have a diagnosis of chronic low back pain for a minimum of 3 months, with an average pain score ≥ 4 on the 11-point (0-10) Numerical Rating Scale (NRS), and to be taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg oral morphine equivalents per day. They were not permitted in the study with evidence of drug or alcohol abuse or a major depressive disorder. Based on other EERW studies of ER opioids, it was estimated that a sample size of 150 subjects per group (300 randomized subjects total) would provide 91% power to detect a treatment difference of 1.0, assuming a standard deviation of 2.6 per group. It was also anticipated that the magnitude of the difference in average daily pain intensity scores between the HC-ER group and the placebo group would be modest, because placebo-treated subjects would not be likely to allow their pain to return to pre-treatment levels, and would go off study and seek alternative pain management once a small increase in pain was experienced.

The study was conducted at 57 sites across all regions of the continental United States between March 2010 and July 2011. The 510 subjects who were enrolled in the study had severe and poorly controlled chronic low back pain, with a mean daily average NRS pain intensity score of 7.0 out of 10, and an average Oswestry disability score of 62 out of 100 despite taking an average of 84 mg of morphine equivalents of opioid analgesics per day. Of the 510 subjects who entered Study 801, 302 (59%) completed the open label conversion/titration phase of the study, where subjects were converted from their previous opioid therapy to HC-ER and then had their HC-ER dose titrated based on pain relief and tolerance to obtain an individual stabilized dose. A total of 124 of the 151 subjects (82%)

who were then randomized to blinded maintenance treatment with HC-ER completed the 12 week study, while only 59 of the 151 subjects (39%) who were randomized to blinded maintenance treatment with placebo completed the study. Meta-analysis showed that the discontinuation rates for adverse events and lack of efficacy in this study were within the range of those observed with other extended-release oral opioids in similarly designed studies.

1.1.1.2 Safety Study 802

ZX002-802 (Study 802) was a multi-center, enriched enrollment, open-label safety study of HC-ER in subjects with chronic pain. Subjects were required to have a diagnosis of chronic pain for a minimum of 3 months requiring an average daily dose of 45 mg oral morphine equivalents per day. They were not permitted in the study with evidence of drug or alcohol abuse or a major depressive disorder. It was estimated that 600 subjects needed to be enrolled to achieve a sufficient sample size to evaluate at least 100 subjects exposed to HC-ER for 1 year and 300 subjects exposed for at least 6 months.

The study was conducted at 56 sites across all regions of the continental United States between June 2010 and December 2011. The 638 subjects who were enrolled in the study had chronic pain conditions that included arthritis (47%), low back pain (38%), and neuropathic pain (30%). Their pain was severe and poorly controlled, with a mean daily average NRS pain intensity score of 6.4 out of 10, and an average Oswestry disability score of 41 out of 100 despite taking an average of 103 mg of morphine equivalents of opioid analgesics per day. Of the 638 subjects who entered Study 802, 424 (66%) completed the open label conversion/titration phase of the study, where subjects were converted from their previous opioid therapy to HC-ER and then had their HC-ER dose titrated based on pain relief and tolerance to obtain an individual stabilized dose. A total of 285 of the 424 subjects (67%) who went on to maintenance treatment with HC-ER completed the 48 week study.

1.1.1.3 Summary of Efficacy

The efficacy of HC-ER compared to placebo was robust across a variety of standard methods for examining pain intensity in clinical trials. For the primary endpoint of Study 801, HC-ER was superior to placebo in the change from Baseline to the end of the study in average daily pain intensity score ($p=0.008$) with a change of 0.5 units on the NRS pain scale for HC-ER treated subjects, and 1.0 units for placebo-treated subjects. HC-ER was also superior to placebo on measures of clinically meaningful individual improvement in pain intensity. For this key secondary endpoint, there were 102 subjects (68%) classified as 30% responders in the HC-ER group (pain score reduced by at least 30%), compared with 47 subjects (31%) in the placebo group. This difference was statistically significant ($p<0.001$), with a much larger proportion of subjects who responded to treatment in the HC-ER group than in the placebo group. Although it was not a prespecified secondary endpoint, there were 72 subjects (48%) classified as 50% responders in the HC-ER group (pain scores reduced by at least 50%), compared with 35 subjects (23%) in the placebo group ($p<0.001$). Response rates of 30%

and 50% are considered "clinically important" and "major" improvements, respectively. Meta-analysis showed that these efficacy results were similar to those observed with other marketed extended-release opioids when studied in standard EERW clinical trials. In addition, subjects on HC-ER had a significantly longer time-to-exit due to loss of efficacy compared to placebo ($p < 0.001$), which is an important and statistically powerful measure of analgesic efficacy. There was also evidence of efficacy in each of the additional domains that are considered important for demonstrating efficacy and effectiveness, when comparing HC-ER to placebo: physical functioning (lower disability scores, $p=0.026$), emotional functioning (lower depression scores, $p=0.006$), and participant ratings of global improvement (greater satisfaction with study medication, $p<0.01$). Efficacy results from study 802 provided supportive confirmation of efficacy, and suggest that HC-ER exerted an effect of pain relief that was sustained over a year of maintenance therapy. The reduction in pain relief was accompanied by indications of improved physical functioning (an increase in the proportion of subjects with disability in the minimal range), with no worsening of emotional function.

1.1.1.4 Summary of Safety

HC-ER was generally safe and well tolerated. The most common treatment-emergent adverse events in chronic pain studies were constipation (15.4%), nausea (13.4%), headache (8.3%), somnolence (7.8%), vomiting (7.1%), back pain (5.7%), and fatigue (5.1%). There were no new or unexpected safety issues revealed, and no indication that HC-ER carries a higher risk of any particular adverse event than either immediate release hydrocodone or other marketed extended-release opioids. The adverse event profile of HC-ER is similar at doses above 100 mg per day to the adverse event profile at doses below 100 mg per day.

1.4 Risk Mitigation and Safe Use of Zohydro ER

In the last two years the federal government has developed broad initiatives to curb the increase in opioid abuse. In 2011 the Office of National Drug Control Policy issued a plan to reduce opioid abuse that addresses initiatives for education, monitoring, proper medication disposal and enforcement. Additionally, FDA has recently approved a class wide REMS for ER/LA opioid analgesics that is directed towards providing training for prescribers and instructions for patients.

The primary risks of Zohydro ER are the same as for other opioid products, namely overdose, abuse and diversion. These risks are associated with inappropriate prescribing, dispensing, use and handling. As a first critically important step, Zogenix is committed to commercializing Zohydro ER in a responsible manner with the goals of achieving safe and appropriate use for people with moderate to severe chronic pain. Zohydro ER will be introduced into the market with a specific strategy intended to focus efforts only on clinicians who are familiar with prescribing extended release opioids for the management of chronic pain. The doses of Zohydro ER, including the highest proposed dosage strength (50 mg) are

substantially less than other currently marketed ER opioids in both putative "abuse-deterrent" and non-abuse-deterrent formulations.

The introduction of Zohydro ER will bring for the first time a form of hydrocodone under the same controls as all other ER opioid products, namely DEA Schedule II, class wide labeling, and the requirements of the recently introduced ER/LA opioid REMS. Recognizing that Zohydro ER as the first single-entity extended release hydrocodone will be a target for abuse and diversion, the risk mitigation initiatives will exceed the basic requirements of the ER/LA opioid REMS in two important areas: 1) broad, yet focused educational initiatives on safe use; and, 2) vigilant oversight of use and abuse patterns.

The overall risk mitigation plan is designed to ensure that prescribers, pharmacists and patients understand the benefit-risk profile and responsible use and handling of Zohydro ER, and that Zogenix is closely monitoring the environment to rapidly detect and respond to concerning signals of abuse, misuse, or diversion. In this context, in addition to the standard ER/LA Opioid REMS, an additional risk mitigation program, the Zohydro ER Safe Use Initiative, is being developed including both internal and external tools and programs to:

- provide surveillance of aberrant drug-related behaviors involving Zohydro ER
- facilitate responsible prescribing of Zohydro ER by targeted, current ER/LA opioid prescribers
- educate all stakeholders – prescribers, patients and pharmacies
- introduce an innovative program, PainCAS, linking patient assessments to prescriber tools for managing patients on Zohydro ER
- assess the effectiveness of these programs

Zogenix acknowledges that participation in voluntary education can be challenging, and has commissioned Inflexxion, an NIH-funded certified addiction education management organization, with the intention of researching methods and approaches to maximizing engagement of the tools and programs. This work has been initiated, and will utilize expertise in this area to achieve the highest level of success.

Key components of the safe-use program are:

- National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) tools that support education through mentoring, skill building, simulations, and provision of clinical relevant information for healthcare providers and patients
- Proprietary programs and materials such as a Prescriber Tool Kit, Pharmacy educational material and a Patient Initiation Kit. The latter will contain access to a safe-keeping product such as a locking cap for the medication bottle and a stand-alone lockbox. This measure is of key importance, as studies have shown that the vast majority of recreational abusers of prescription opioids obtain their product from family members without their knowledge (Becker 2011).
- Support and promote community opioid disposal programs

- Piloting innovative programs such as prescriber mentoring and access to urine drug screening services
- NAVIPPRO surveillance systems to provide an ongoing assessment of Zohydro ER abuse across various populations in real time
- Oversight from an independent Safe Use Advisory Board to assist the company in interpreting the results of surveillance activities, results of knowledge, attitudes and behavior surveys, and other data. To ensure the timely escalation of critical safety information, the Safe Use Advisory Board will have direct access to the Zogenix Board of Directors and will be authorized to report the results of their deliberations directly to the FDA if they choose to do so.

These systematic measures are being put in place to ensure the introduction of Zohydro ER meets the highest standards of integrity, concern and commitment for safe use of the product while at the same time ensuring the availability of the appropriate medications for patients suffering from chronic pain.

1.5 Benefit / Risk Profile

Zogenix recognizes the wide-scale public health issue of abuse, misuse and diversion of opioids, the wide-scale public health issue of intractable chronic pain, and the struggle to achieve a balanced use of opioid analgesics with which many stakeholders have grappled, including this Advisory Committee.

The clinical benefits of Zohydro ER include pain relief, reduction in disability and increased patient satisfaction with pain medication. Other benefits include the availability of hydrocodone in extended release form when chronic pain patients are first converted from a regimen of immediate release HC/APAP, and the addition of Zohydro ER to prescribers' choices when there is a need to change from one extended-release opioid to another for reasons of tolerability or falling efficacy. Finally, hydrocodone will be available for the first time without acetaminophen for patients who are sensitive to acetaminophen hepatic toxicity, or require hydrocodone doses that do not allow safe dosing with HC/APAP. The risks include opioid adverse events, accidental overdose with therapeutic usage, and addiction, unintentional overdose and death from inappropriate prescribing, diversion, misuse, and abuse. Measures that are expected to reduce risk include a Schedule II prescribing status, the FDA's new ER/LA opioid REMS program, and the Zohydro ER Safe Use Initiative program.

The rigorous and vigilant oversight and compliance program that was undertaken and executed during the registration clinical program is representative of the company's attitudes and planned philosophy for marketing Zohydro ER. Zogenix believes that there is a strong medical need for this product, but that it must be introduced into clinical usage with appropriate safeguards and oversight. The company's experiences and policies during the clinical trials represent an excellent framework of responsible prescribing, vigorous training and education, and vigilant oversight with immediate and aggressive corrective actions that foreshadows the Zogenix approach to commercializing Zohydro ER in the most responsible manner possible.

In conclusion, the data presented in this Briefing Document demonstrate that Zohydro ER is effective in relieving chronic pain. The safety profile of Zohydro ER was consistent from the two largest studies, and was consistent with the safety profiles of other opioid medications with no new or unexpected toxicities observed. Zogenix is committed to a conservative commercialization strategy while making real progress in understanding the value of different approaches to mitigating risks. Overall the benefits of Zohydro ER for patients exceed the risks associated with this new formulation, in the context of a responsible Zohydro ER commercialization plan.

2 INTRODUCTION

HC-ER, proposed trade name Zohydro ER, is an orally administered, ER formulation of hydrocodone. It has been developed for the management of moderate to severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time. The analgesic efficacy and safety of hydrocodone is well known through decades of clinical use of combination products for the treatment of pain, but it has never been available in the United Sates (US) as a single-agent product. To support treatment of patients with chronic moderate to severe pain, Zohydro ER was developed without acetaminophen (APAP) in an ER formulation that enables twice daily (q12h) administration.

Zogenix has completed a non-clinical, pharmacology, and clinical program for Zohydro ER that FDA agreed was sufficient for its New Drug Application (NDA). This briefing document outlines the development program for Zohydro ER, which has shown Zohydro ER to be safe and effective for the treatment of chronic, moderate to severe pain. Recognizing the wide-scale public health issue associated with abuse, misuse and diversion of opioids, Zogenix is committed to the safe use of Zohydro ER. The briefing document outlines the basic requirements, consistent with other ER/LA opioids, of the FDA-required Risk Evaluation and Mitigation Strategy (REMS) for Zohydro ER and additional voluntary risk mitigation programs being implemented to specifically and proactively address the primary risks of misuse, abuse, diversion, inappropriate prescribing, and unintentional overdose. Collectively, these measures are designed to ensure that the important benefits of Zohydro ER seen in patients with chronic moderate to severe pain outweigh the risks.

2.1 Background for Development of Zohydro ER

2.1.1 Disease Burden of Chronic Pain

The International Association for the Study of Pain defines chronic pain as “pain that persists beyond an expected time frame for healing” (Merskey 1994). CLBP is the most common cause of disability in industrialized nations. Other common types of chronic non-cancer pain include arthritis pain, headache, neuropathic pain, and fibromyalgia (National Institute of Neurological Disorders and Stroke, National Institute of Health [NIH] Chronic Pain Information Page). Approximately 100 million adults in the US are affected by chronic pain (Institute of Medicine, 2011). Several studies have shown an increase in the prevalence of chronic pain over time (Manchikanti 2012a; Freburger 2009; Harkness 2005). In the US adult population, it is estimated that 19% of the adult population has chronic spinal pain, with 29% reporting lifetime prevalence (Von Korff 2005).

Chronic pain has a profound impairment on a person’s physical activity, social, and emotional well-being and psychological health. Patients with chronic pain frequently report having anxiety and depression (Arnow 2006; Von Korff 2005; Elliot 2003; Dersh 2002). Study results showed that patients with chronic pain have a decreased health related quality of life (HRQL) compared with patients without chronic pain (Arnow 2006; Elliot 2003). Comorbid conditions associated with chronic pain conditions are mental disorders, other chronic pain conditions, heart disease, and diabetes (Von Korff 2005). Annual costs associated with chronic pain in US are estimated to be $560-635 billion; which includes the

cost of health care ($261-300 billion) and productivity lost ($297-336 billion) (Institute of Medicine, 2011). Thus chronic pain is one of the major public health crises of our time.

2.1.2 Management of Chronic Pain Using Opioids

There are many barriers to effective management of chronic pain. These can include treatment, education, policy gaps, and the extent of evidence-based research. To address some of these barriers, the Institute of Medicine Committee Advancing Pain Research, Care, and Education released a Blueprint for Transforming Prevention, Care, Education, and Research for Reliving Pain in America (Institute of Medicine, 2011). The goal of the report was to "gain a better understanding of pain of all types and improving efforts to prevent, assess, and treat pain".

Chronic pain of most types is generally managed first by the patient at home, using a variety of self-care strategies including judicious modification of physical activities, improved sleep hygiene, ice and heat, appropriate splinting, over-the-counter topical treatments, and, in a large proportion of patients, complementary treatments such as acupuncture, chiropractic, homeopathy, and herbal remedies. Regular use of over-the-counter analgesics is widespread, including acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). When these approaches are inadequate patients will seek medical care, typically with a primary care physician. The typical primary care approach consists of more formalized approaches to physical modalities (e.g. physical therapy, prescribed exercise regimens) and regular use of prescription "simple" analgesics: again acetaminophen and NSAIDs. Unfortunately these approaches yield adequate relief of symptoms and restoration of function in only a minority of sufferers, and the "simple" analgesics have created their own pandemics of toxicity: in the case of acetaminophen hepatic dysfunction (see below) leading in many cases to liver transplantation, and in the case of NSAIDs, thousands of deaths per year due to gastrointestinal and other types of bleeding, exacerbations of congestive heart failure, and renal toxicity, among others. Thus, a large proportion of the millions of Americans seeking pain relief, restoration of function at work and at home, and improvement in quality of life diminished by chronic pain, fail to obtain relief with the standard "conservative" approaches, which in many cases are far from conservative.

2.1.3 The Role of Opioids in the Management of Pain

The efficacy of opioids in the treatment of chronic pain has been established beyond doubt in several robust meta-analyses (Eisenberg 2005; Furlan 2006; Papaleontiou 2010; Noble 2010) of studies in a variety of chronic pain types.. The strength of the evidence base behind opioid therapy for chronic pain exceeds that of any other class of analgesic, with the possible exception of the NSAIDs, which are limited in efficacy to musculoskeletal pain. On the other hand, opioids are regarded as the only broad spectrum analgesic, effective in virtually every type of pain in which they are rigorously studied. Furthermore, the effect size of opioids in the treatment of chronic pain exceeds that of any other marketed analgesic class, which has been demonstrated in both head-to-head studies and meta-analyses.

While it is often claimed that there are no long-term studies of the efficacy, or effectiveness, of opioid analgesics, this is not true. Portenoy (2007) published a 3-year prospective study of

the use of extended-release oxycodone for chronic pain, showing that a substantial proportion of patients maintained good responses over extended periods of time. A randomized, double-blind, placebo-controlled study of tapentadol and oxycodone extending for a year has been reported, with both treatments demonstrating efficacy (Wild 2010). A small randomized controlled study of flexible-dose opioids, fixed-dose opioids, and NSAIDs over one year has been published, with both opioid groups showing superiority over NSAIDs (Jamison 1998). A prospective randomized controlled study of over 11,000 patients, followed for a year, compared hydrocodone, tramadol, and NSAIDs, with the major focus on establishing the relative abuse rate of these products (Adams 2006). Finally, there are numerous one-year open-label extension studies, required for regulatory approval, of various opioid analgesics that generally show meaningful sustained pain relief in between one-third and one-half of patients.

The role of opioids in the management of chronic pain has been recognized by numerous professional organizations, after careful and critical examination of the body of evidence. These include the American Pain Society, the American Geriatric Society, and the American College of Rheumatology

If all of this is true, why are opioids so controversial (Katz, 2007)? The primary reason is the specter of inappropriate and harmful behaviors and consequences among users of opioids, both patients prescribed the medication and individuals who acquire it specifically for the purpose of abuse. Evidence is a key tool in the hands of those who would seek a rational policy position on opioid use, and useful evidence about the risks of opioid abuse has emerged in recent years. A large randomized controlled study of over 11,000 patients published in 2006 (Adams 2006) has quantified the rate of abuse among patients assigned to receive either immediate-release hydrocodone, tramadol, or NSAIDs for a one year observation period. This landmark study provides the first credible estimate of abuse rates from a prospective patient study, which was approximately 5% for the hydrocodone group, and approximately 2% in the tramadol and NSAID groups. Note that although there are over 100 million prescriptions for hydrocodone annually in the US, only a small percentage of these patients will progress to chronic hydrocodone use at a sufficient dose to justify an ER opioid formulation – therefore the total burden of abuse generated *among patients* by an ER hydrocodone product is likely to be small (not to diminish the importance of risk management procedures).

Among non-patients in the community who obtain prescription opioids illicitly for the purpose of abuse, all mu agonist opioids have similar abuse rates when appropriately adjusted for potency and availability (Dasgupta 2006), as expected from the basic pharmacology of mu agonist opioids. (It should be noted that overdose mortality may be excessive for certain opioids, particularly methadone, likely due to difficult-to-manage pharmacokinetics [PK] and potentially direct cardiotoxicity). The implication of this observation is that the absolute rate of abuse of a mu agonist opioid will depend directly on how widely it is used. Hydrocodone is a noteworthy example of this phenomenon: it is by far the most widely prescribed opioid and unsurprisingly has the highest absolute abuse rate; the expectation is that shifting prescribing to alternative opioids would simply increase the abuse rate of those products with no net public health impact.

In summary, opioids have been indisputably demonstrated to be efficacious and safe for the treatment of acute and chronic pain, by any applicable standard. Yet, widespread opioid abuse and overdose fatalities continue to cloud the risk-benefit profile of these agents. The societal challenge now is to find a middle ground which ensures the availability of these medications to those who need them, while more effectively mitigating their risks to both patients and non-patients, until such time as drug discovery and development efforts generate a truly "abuse deterrent" strong analgesic.

2.1.4 Medical Need for Zohydro ER

Both IR and ER formulations of opioids are marketed in the United States. Except for hydrocodone, all orally-administered opioids exist in both IR and ER formulations. For patients on chronic opioid therapy, an ER formulation may be advantageous by improving dosing convenience and treatment adherence with the benefit of more consistent steady-state plasma levels of the drug. Patients who tend to benefit from ER opioids are those with pain around-the-clock, significant pain interference with sleep, pain upon morning awakening, and need for short-acting medication every few hours. Responsiveness to opioids varies greatly among individuals and as a result, dose titration is necessary for each subject to balance the analgesic effect with side effects, and patients frequently find a meaningful therapeutic index from one opioid but not others. Therefore, once a patient has settled on an opioid, such as hydrocodone, if that patient would benefit from the addition of an ER product, using the same molecule is generally recommended. Ironically, hydrocodone is the most widely prescribed opioid for both acute and chronic pain (Kelly 2008), but is the only opioid without an ER formulation to date.

Hydrocodone is a phenanthrene derivative opioid analgesic with multiple actions qualitatively similar to those of codeine. The most frequently prescribed analgesic form is with acetaminophen (HC/APAP such as Vicodin), but it is also available in combination with ibuprofen. The majority (>98%) of prescriptions for hydrocodone combination products are dispensed for HC/APAP. As a consequence of its wide availability (over 106 approved products approved in the US), physician familiarity, and less stringent scheduling (DEA Schedule III), HC/APAP is the most prescribed opioid product, and in fact the most frequently filled prescription in the US, with over 136 million prescriptions in 2011.

When excessively or improperly used, APAP can lead to liver damage and acute liver failure. Data presented at an FDA advisory committee in 2009 and reviewed recently (Michna 2010) showed that APAP overdose was the leading cause of acute liver failure in the US, and that 63% of the unintentional overdoses were associated with ingestion of opioid/APAP combination products. Although there is no evidence that hydrocodone causes these cases of hepatic failure, it seems likely that some of the excessive APAP dosing is driven by a need for larger doses of hydrocodone once tolerance develops, and since hydrocodone is not available as single agent, patients self-treat their pain by taking ever higher and excessive doses of HC/APAP. The FDA Advisory Committee voted (20-17) to recommend removal of opioid/APAP combinations from the market. However, it was noted at the meeting that, without a single-agent hydrocodone available, elimination of these medications could have deleterious consequences on the practice of pain management (Michna 2010). Subsequent

commentary by Fishman and Gilson (2010) indicated the clinical need for a marketed single-entity hydrocodone product for treating moderate to severe pain.

The availability of a single-entity hydrocodone for moderate to severe pain would circumvent the concerns of inadvertent APAP overdose associated with the use of HC/APAP combination products for patients requiring higher doses of hydrocodone to achieve effective pain relief.

An individual patient's response to a given opioid is difficult to predict, both in terms of analgesic effectiveness, and in terms of tolerability, particularly due to side effects. Part of this phenomenon is due to opioid tolerance. In addition, it has also been shown that levels of activation of mu-opioid receptor subtypes vary from one patient to the next with usage of the same opioid analgesic, and vary in the same patient when receptor activation is compared between two different opioid analgesics (Pasternak 2001). This is probably a major reason for the clinical observation that patients are only partially cross-tolerant to both efficaciousness and side effects when changed from one opioid analgesic to another.

Clinical guidelines support opioid rotation (changing from one opioid to another opioid) in patients on chronic opioid therapy who are unable to maintain therapeutic goals with their current opioid (Chou 2009). The pharmacological basis of opioid rotation is considered related to incomplete cross-tolerance to the analgesic and non-analgesic responses between opioids, which could potentially result in a better balance of analgesic and side effects when one opioid is changed for another (Slatkin 2009). While well controlled studies are lacking, opioid rotation is considered a necessary clinical practice in the management of chronic pain (Fine and Pynsent, 2009; Slatkin 2009; Nalamachu 2011), and up to 30% of patients will require opioid rotation at some time (Slatkin 2009). This practice provides a rationale for having another opioid available to clinicians treating patients with chronic pain with ER opioids.

For the same reasons, physicians are taught to attempt to stay with the same opioid when a patient is being converted from short-term opioid therapy with IR agents to long-term or chronic treatment with ER opioid analgesics. Changing opioid at the time of conversion may complicate the physician's assessment of the treatment program, as outcomes from the PK of the ER analgesic may become confused with outcomes caused by cross-tolerance issues. Hydrocodone is the most commonly used opioid analgesic for treatment of acute pain, and it is also commonly used as the first-line opioid for chronic pain. There is strong demand from physicians to have hydrocodone available for these patients as their first ER opioid for management of chronic pain. Conversion to Zohydro ER would also facilitate an increase in hydrocodone dose unencumbered from the concerns of APAP.

In summary, the need for an ER formulation of hydrocodone is:

- For patients on immediate-release hydrocodone who need an extended release product, and in whom it makes sense to stay with the same molecule
- For patients who have hepatic compromise and are at risk for further hepatic injury from APAP

- And for patients on other ER opioids in whom another option for opioid rotation is of value.

2.2 Zohydro ER Product Profile

2.2.1 Spheroidal Oral Drug Absorption System (HC-ER)

The dosage form for HC-ER was developed using the Alkermes SODAS (Spheroidal Oral Drug Absorption System) technology, which is comprised of drug-containing multi-particulates contained in a hard gelatin capsule. The SODAS technology is based upon initially coating sugar spheres with the drug substance and suitable excipients to form IR multi-particulates. Sustained-release (SR) multi-particulates are then prepared by coating the IR multi-particulates with rate-controlling polymers to obtain a desired dissolution profile. The target dissolution rate for the Zohydro ER product is then achieved by combining IR beads with SR beads in a defined active ratio, followed by encapsulation to the desired product strength of 10, 15, 20, 30, 40, or 50 mg of hydrocodone bitartrate in hard gelatin capsules. The advantage of this delivery system is that plasma drug concentrations are reached relatively quickly, and sustained for at least 12 hours because of a biphasic absorption profile. Generally, multi-particulate systems tend to be less prone to inter- and intra-subject differences in gastric emptying and small intestinal transit times than ER monolith tablet formulations. They result in more consistent PK of the drug and are less impacted by extrinsic factors, such as food.

The SODAS technology is an established technology used in 6 marketed products in the US. Three of the approved products are distributed under DEA Schedule II and include Avinza® (morphine sulfate ER), Ritalin® LA (methylphenidate), and Focalin XR® (dexmethylphenidate hydrochloride).

The Zohydro ER formulation does not contain abuse deterrence features. Out of the more than 30 branded or generic ER/LA products containing morphine, oxycodone, oxymorphone, hydromorphone, tapentadol, buprenorphine, fentanyl, or methadone, only three products have putative abuse deterrent features (OxyContin, Opana ER, and Nucynta ER). Zogenix believes that the technology around abuse deterrent formulations is continuing to evolve, and that effective abuse deterrence must critically include active programmatic efforts at risk reduction. Section 6 contains an extensive description and discussion of the risk mitigating activities and programs that Zogenix will implement to ensure that Zohydro ER is used as safely as possible.

2.2.2 Proposed Indication and Use

Zohydro ER is indicated for the management of moderate-to-severe chronic pain for patients when a continuous around-the-clock opioid analgesic is needed for an extended period of time.

Zohydro ER is not intended for the following uses: 1) on an as-needed basis, 2) during the immediate postoperative period, or 3) if the pain is mild, or not expected to persist for an extended period of time.

Since the risks of HC-ER and its potential to be abused, misused, or diverted are similar to those of all Schedule II long-acting opioid analgesics, the proposed labeling for Zohydro ER contains opioid class labeling, particularly in the Black Box Warning, Warnings and Precautions, and Drug Abuse and Dependence sections.

2.2.3 Proposed Dosage and Administration

The proposed dosage strengths of Zohydro ER are 10, 15, 20, 30, 40, or 50 mg capsules administered twice daily every 12 hours with or without food. As with other opioid analgesics used to treat chronic pain, the dose of Zohydro ER should be individually titrated for each patient to optimize the balance between adequate analgesia, while minimizing unwanted non-analgesic effects.

2.2.4 Proposed Initiation of Therapy

It is critical to individualize the dosing regimen for each patient. In selecting the initial dose of Zohydro ER, attention should be given to the following:

- The risk factors for abuse or addiction, including whether the patient has a previous or current substance abuse problem, a family history of substance abuse, or a history of mental illness or depression;
- The age, general condition, and medical status of the patient;
- The patient's opioid exposure and opioid tolerance (if any);
- The daily dose, potency, and kind of the analgesic(s) the patient has been taking;
- The reliability of the conversion estimate used to calculate the dose of HC;
- The type and severity of patient's pain;
- Other non-opioid analgesics that they may be taking; and
- The balance between pain control and adverse reactions.

2.2.5 Conversion to Zohydro ER in Patients Currently on Opioid Therapy

The suggested approach for converting from existing opioid therapy to Zohydro ER is as follows:

- Discontinue all other around-the-clock opioid drugs when Zohydro ER therapy is initiated.
- Refer to published relative potency information (also provided in the proposed Prescribing Information) to calculate the hydrocodone total daily dose (TDD).
- For patients on a regimen of mixed opioids, calculate the approximate oral hydrocodone dose for each opioid and sum the totals to estimate the total daily hydrocodone dose.
- Decrease the calculated conversion dose of hydrocodone by 20%-30% and divide by 2 to determine the twice daily dose of Zohydro ER
- Round down, if necessary, to the appropriate Zohydro ER capsule strengths.
- Close observation and frequent titration are indicated until patients are stable on the new therapy.

2.3 Regulatory Summary

The Investigational New Drug (IND) Application (IND 65,111) for Zohydro ER was submitted by Elan Corporation (now Alkermes) on 25 June 2002. Zogenix acquired the US rights to Zohydro ER from Elan in November 2007, and the IND for Zohydro ER was transferred to Zogenix on 31 January 2008. Zogenix held an End-of-Phase 2 meeting with FDA on 5 May 2008 where agreement was reached on nonclinical, clinical, and Chemistry, Manufacturing and Controls elements for further development. In particular, it was agreed that the regulatory approval for Zohydro ER could follow a 505(b)(2) NDA pathway, and would require only a single well-controlled efficacy study in a CLBP population, together with an open-label safety study in subjects with chronic pain to generate sufficient subject exposures for the NDA safety database of at least 300 subjects on HC-ER for 6 months and at least 100 subjects on Zohydro ER for 1 year. Following completion of the Phase 3 clinical program, Zogenix held pre-NDA meetings with FDA on 17/18 November 2011 and the NDA for Zohydro ER was submitted on 01 May 2012.

3 NONCLINICAL DEVELOPMENT PROGRAM

3.1 Nonclinical Studies

Hydrocodone bitartrate has a long clinical history in numerous combination drug products for pain and cough control. The efficacy and safety in humans for the labeled uses of these products have been well established. As part of the Zohydro ER NDA submission to support the safety for hydrocodone bitartrate, studies were conducted to address pre-existing data gaps with respect to genotoxicity and reproductive toxicology; to evaluate acute and chronic toxicology of hydrocodone bitartrate, as well as the Zohydro ER formulation; and to qualify potential impurities. An outline of the overall nonclinical PK and toxicology studies conducted for the Zohydro ER NDA is shown in Table 1. Nonclinical information was also summarized from the literature, and from the reference approved NDA product, Vicoprofen.

Table 1: Completed Nonclinical Studies Conducted with Hydrocodone Bitartrate

Study Type and Duration	Route of Administration	Species/Model	Doses
PHARMACOKINETICS			
Single-Dose Pharmacokinetics[a]	Oral	Rats	25, 75 mg/kg
Single-Dose Pharmacokinetics[a]	Oral	Rabbits	10, 100 mg/kg
ACUTE TOXICOLOGY			
Acute Oral Toxicity Study (14-day Observation Period)	Oral	Rats	0, 3, 10, 30 mg/kg
Acute Oral Toxicity (14-day Observation Period)	Oral	Dogs	0, 3, 10, 30 mg/kg
REPEAT DOSE TOXICOLOGY			
5-Day Toxicity Study[a] (Dose-Range)	Oral	Rabbit	0, 1, 5, 10, 25, 50, 75, 150, 300 mg/kg/day
14-Day Toxicity Study[a] (Dose-Range)	Oral	Mouse	0, 5, 25, 50, 100 mg/kg/day
28-Day Toxicity Study	Oral	Rats	0, 3, 10, 30 mg/kg/day
28-Day Toxicity Study	Oral	Dogs	0, 3, 10, 30 mg/kg/day
28-Day Toxicity Study	Oral[a]	Dogs	0, 3.2, 13.5, 41.4/ 30.0

Study Type and Duration	Route of Administration	Species/Model	Doses
			mg/kg/day
90-Day Toxicity Study	Oral	Mouse	0, 5, 25, 75, 150 mg/kg/day
90-Day Toxicity Study	Oral	Rats	0, 5, 25, 50, 100 mg/kg/day
GENOTOXICITY			
In Vitro Bacterial Reverse Mutation Assay	In vitro	*S. typhimurium* and *E. coli* strains	2.5, 7.5, 25, 75, 200, 600, 1800, 5000 µg/plate
In Vitro Mammalian Chromosomal Aberration Study	In vitro	Chinese Hamster Ovary cells	625, 1250, 2500, 5000 µg/mL
In Vivo Mammalian Erythrocyte Micronucleus Assay	Intraperitoneal	Mouse	0, 15, 30, 60 mg/kg
REPRODUCTIVE TOXICOLOGY			
Fertility and General Reproductive Behavior (Segment 1)	Oral	Rats	0, 25, 75, 100 mg/kg/day
Embryo-Fetal Toxicity (Segment 2)	Oral	Rats	0, 1, 5, 10, 25, 75, 100 mg/kg/day
Pre- and Post-Natal Development (Segment 3)	Oral	Rats	0, 1, 25, 75, 100 mg/kg/day
Embryo-Fetal Toxicity[a] (Dose-Range Segment 2)	Oral	Rabbits	0, 25, 75, 100 mg/kg/day
Embryo-Fetal Toxicity (Segment 2)	Oral	Rabbits	0, 25, 50, 75 mg/kg/day

All studies with the exception of the single-dose pharmacokinetic and 14-day mouse, 5-day rabbit, and Segment 2 rabbit dose-range studies were conducted in compliance with Good Labor Practice regulations.
[a] Zohydro ER capsules administered

There were no unexpected findings from the nonclinical research program. Hydrocodone exerted the expected effects for a mu opioid agonist. Overall, the collective data derived from the repeat-dose general toxicology studies provide no indication that the administration of hydrocodone bitartrate as a single entity would result in adverse clinical events, other than those reported or attributable to this agent in the currently-marketed combination products. Based on the long history of human use of hydrocodone bitartrate in various combination drug products, the available safety data, and information from clinical use of opioids including hydrocodone in public domain sources, as well as Zogenix's aforementioned comprehensive Good Laboratory Practice toxicology studies and results, Zogenix believes that Zohydro ER capsules can be labeled for safe use in humans.

3.2 Status of Carcinogenicity Studies

Zogenix and FDA agreed that the results of carcinogenicity studies would be a post-approval requirement, provided the studies were initiated prior to NDA submission. The final carcinogenicity study protocols for two rodent species were reviewed and approved by the FDA/CDER/Executive Carcinogenicity Assessment Committee on 04 March 2011. Carcinogenicity studies (24-month) in rats and mice were initiated in January 2012.

4 PHARMACOLOGY AND BIOPHARMACEUTICAL DEVELOPMENT

4.1 Summary of Pharmacology and Biopharmaceutical Studies

Eight clinical pharmacology studies were conducted to evaluate the bioavailability, PK, and pharmacodynamics of HC-ER (Table 2). The results of the key studies are described in this overview of biopharmaceutics and clinical pharmacology.

Table 2: HC-ER Clinical Pharmacology Studies (Phase 1 and 2)

Study No.	Type of Study
SINGLE-DOSE STUDIES	
ELN-0901001	Bioavailability of 20 mg Hydrocodone from Hydrocodone bitartrate formulation relative to Vicodin HP tablets in 18 healthy volunteers
ZX002-1102	Bioequivalence of 30 mg HC-ER formulation relative to Vicoprofen
ELN-0302002	Pharmacokinetics of 20 mg HC-ER formulation administered with and without food in 12 healthy volunteers
ZX002-0901	Bioavailability, safety and pharmacokinetics of 50 mg HC-ER formulation with 0%, 20%, 40% alcohol without food in 30 healthy volunteers
ZX002-1001	Pharmacokinetics and safety of 20 mg HC-ER formulation in 30 subjects with hepatic insufficiency
ZX002-1002	Pharmacokinetics and safety of 20 mg HC-ER formulation in 37 subjects with renal insufficiency
ELN-154088-201	Pharmacokinetics, safety and efficacy of 10 to 40 mg HC-ER formulation in 241 subjects following bunionectomy surgery
MULTIPLE-DOSE STUDIES	
ELN-154088-203	Multiple-dose pharmacokinetics of HC-ER formulation in 37 subjects with chronic osteoarthritis pain

HC-ER = hydrocodone extended-release.

4.2 Pharmacokinetics

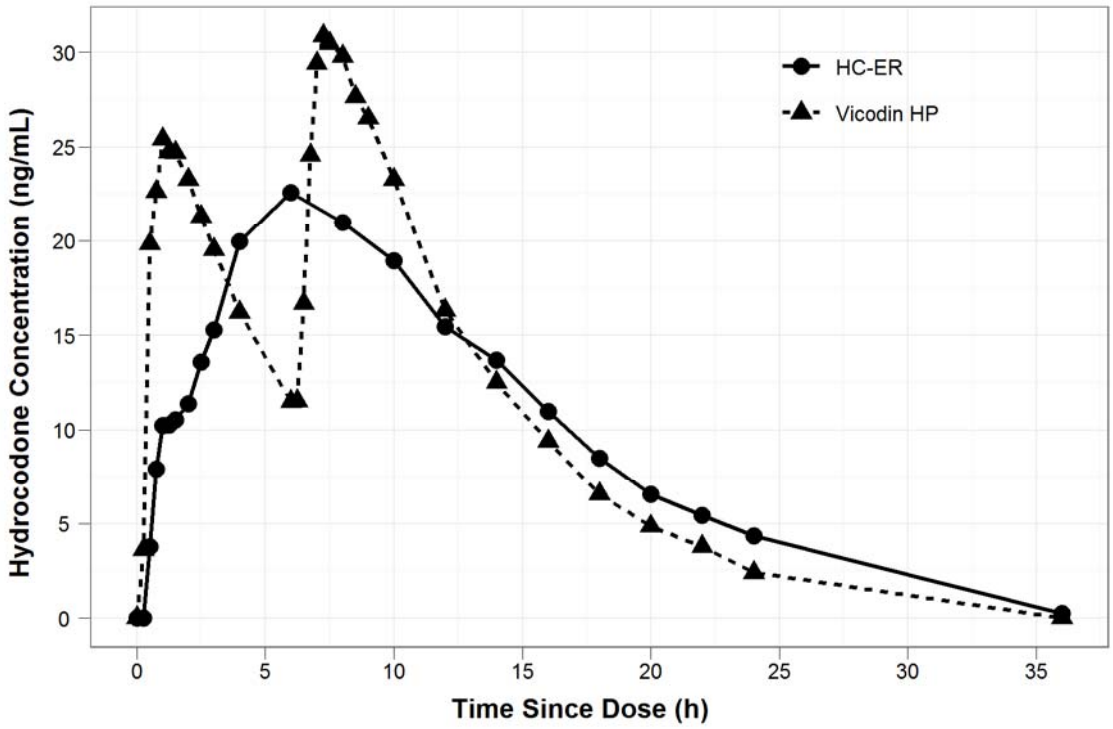
4.2.1 Single-dose Studies

Single dose studies have evaluated the PK of HC-ER versus HC/APAP and HC/ibuprofen combination tablets. Overall, the PK profile of HC-ER is characterized by a biphasic absorption profile as a result of hydrocodone release from the two available populations of beads in the formulation. The small portion of hydrocodone contained in the IR beads is absorbed at a similar rate to hydrocodone from HC/combination products. Thereafter, the absorption of hydrocodone is slower than from HC/combination tablets, indicating that drug absorption is being controlled by the release of hydrocodone from the ER beads.

The PK of HC-ER was compared to HC/APAP in a Phase 1, parallel group, open-label study (ELN-0901001). The study compared a 20 mg dose of HC-ER with the same hydrocodone dose given in divided doses 6 hours apart from a marketed HC/APAP product (Vicodin HP). The mean hydrocodone plasma profiles are provided in Figure 1 and mean PK parameters are shown in Table 3. The study showed that the bioavailability of HC-ER, based upon $AUC_{0\text{-last}}$, was comparable to that of HC/APAP. As expected the mean C_{max} was lower in subjects receiving HC-ER, despite the fact that the corresponding dose of hydrocodone in

HC/APAP was divided into two doses given 6 hours apart. The mean T_{max} for hydrocodone was later in subjects receiving HC-ER.

Figure 1: Mean Hydrocodone Plasma Concentration-Time Profiles Following Administration of HC-ER and Two Doses of HC/APAP (Vicodin HP) (adapted from ELN-0901001 CSR, Figure 14.2.1.3.1)



HC-ER = hydrocodone extended-release.

Table 3: PK Parameters of HC-ER Compared to Vicodin HP (Study ELN-0901001)

Parameter	Statistic	HC-ER 20 mg n=9	Vicodin HP 20 mg n=16
C_{max} (ng/mL)	Mean (SD)	23.2 (3.41)	28.8 (6.60)[b]
	CV%	14.7	23.0
$AUC_{0\text{-last}}$ (ng·h/mL)	Mean (SD)	322 (56.0)	339 (58.3)
	CV%	17.4	17.2
T_{max} (h)	Mean (SD)	7.33 (1.41)	0.97 (0.50)[b]
	CV%	19.3	51.3
Relative bioavailability (%)[a] (based on $AUC_{0\text{-last}}$)	Mean (SD)	97.8 (7.93)	----
	CV%	8.10	----

[a] Reference was Vicodin HP
[b] primary (first) peak data
HC-ER = hydrocodone extended-release; PK = pharmacokinetic.

The 505(b)(2) NDA for HC-ER requires cross-reference to the established safety and efficacy of a hydrocodone product approved under an NDA, which is Vicoprofen in this case. The formal bioavailability/bioequivalence bridging study for the submission compared HC-ER to Vicoprofen tablets (7.5 mg HC/200 mg ibuprofen) in a Phase 1, randomized, open-label, two-period crossover study (ZX002-1102). In this study HC-ER was administered as a single 30 mg dose at time zero whereas Vicoprofen was administered as four tablets; two tablets at time zero and two tablets at 6 hours post initial dose. Bioequivalence analysis of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ derived from hydrocodone concentrations showed that the 90% confidence interval (CI) for the least-square (LS) geometric mean ratios for overall exposure ($AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) were contained within the bioequivalence limit of 80%–125% while those for C_{max} were not (Table 4). These results indicate that the extent of absorption is comparable between HC-ER and Vicoprofen; the rate of absorption is slower with HC-ER, consistent with the intended absorption profile of the formulation, which results in lower peak hydrocodone concentrations.

Table 4: Bioequivalence Comparison of Hydrocodone $AUC_{0–24}$, $AUC_{0–inf}$, and C_{max}, PK-Bioequivalence Population

Parameter	Statistic	HC-ER vs. Vicoprofen (N=13)
$AUC_{0–last}$ (ng·h/mL)		
	Geometric Mean Ratio (%)	91.1
	90% CI	82.8, 100
$AUC_{0–inf}$ (ng·h/mL)		
	Geometric Mean Ratio (%)	93.2
	90% CI	84.5, 103
C_{max} (ng/mL)		
	Geometric Mean Ratio (%)	68.7
	90% CI	63.2, 74.6

CI = confidence interval.

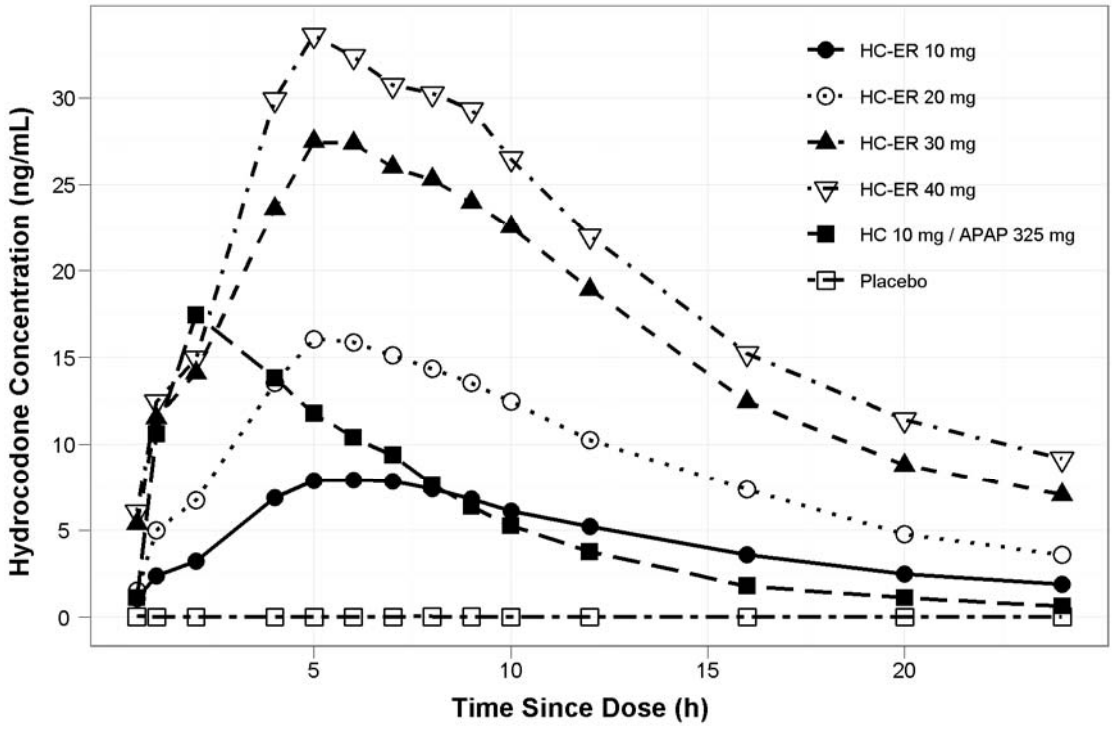
The PK of different dosage strengths of HC-ER against a reference treatment (10 mg HC/325 mg APAP tablets) was assessed in Study ELN154088-201. This was a multicenter, randomized, double-blind, parallel group, single dose, placebo controlled, active-comparator study in subjects following bunionectomy surgery. HC-ER dosage strengths of 10, 20, 30 and 40 mg were evaluated together with the reference treatment. The mean hydrocodone PK plasma profiles for the PK-evaluable group (n=115) are shown in Figure 2. Single-dose PK parameters for hydrocodone from HC-ER in these bunionectomy subjects were comparable to those previously observed in healthy subjects. In general, C_{max} and $AUC_{0\text{-last}}$ estimates for hydrocodone increased linearly with dose and support the presence of dose proportionality across the 10-40 mg dose range of HC-ER (Table 5).

Table 5: Assessment of Dose Proportionality Based upon Hydrocodone PK Parameters, Study ELN154088-201

Parameter[a]	Statistic[b]	10 mg n=21	20 mg n=19	30 mg n=19
C_{max}	Ratio	0.947	0.929	1.11
	90% CI	0.816 – 1.10	0.797 – 1.08	0.955 – 1.30
$AUC_{0\text{-last}}$	Ratio	0.942	0.899	1.11
	90% CI	0.807 – 1.10	0.768 – 1.05	0.951 – 1.31

[a] Parameters were dose-normalized for comparison
[b] Ratio and 90% CI were calculated relative to the 40 mg dose
CI = confidence interval; PK = pharmacokinetic.

Figure 2: Mean Plasma Hydrocodone Concentration-Time Profiles for 10, 20, 30, and 40 mg HC-ER (Study ELN-154088-201 CSR, Figure 7)



4.2.2 Multiple-dose Study

The steady state characteristics of HC-ER were determined in a multi-center, randomized, open-label, multiple-dose, two group, dose-escalation study in subjects with chronic moderate-to-severe osteoarthritis (OA) pain (Study ELN 154088-203). Subjects in Group 1 were initially dosed with 10 mg of HC-ER (q12h) and had their study medication increased by 10 mg every week for three weeks. Subjects in Group 2 were initially dosed with 20 mg of HC-ER (q12h) and followed the same dosing interval increase as Group 1. The PK of hydrocodone were followed on Day 1 (i.e. initiation of dosing) and then at steady-state on Days 7, 14, and 21 (i.e. after one week of a receiving a constant HC-ER dose). The

steady-state PK profiles are shown in Figure 3. The derived PK parameters are listed in Table 6 and the results of the dose proportionality analysis are provided in Table 7.

For hydrocodone and norhydrocodone, all of the 90% CIs for the C_{max} and AUC_{0-12} ratios fell with the acceptable range for bioequivalence (0.80 to 1.25) indicating statistically significant dose proportionality. The relatively flat PK profiles of hydrocodone after HC-ER administration shown in Figure 3 are supported by the results shown in

Table 8. $C_{ss,avg}$ values were all ~20% lower than mean C_{max} values and peak-to-trough fluctuation was relatively low (approximately 50 to 60%).

Steady-state values (Day 7) for C_{max} and AUC_{0-12} were approximately two-fold higher than the corresponding values for Day 1 after administration of 10 or 20 mg of HC-ER. Specifically, the mean AUC_{0-12} increased from 82.3 ng·hr/mL on Day 1 to 169 ng·hr/mL on Day 7 in the Group 1 subjects who received 10 mg; the mean AUC_{0-12} increased from 171 ng·hr/mL on Day 1 to 354 ng·hr/mL on Day 7 in the Group 2 subjects who received 20 mg.

Table 6: PK Parameters of HC-ER at Steady State – Study ELN-154088-203

		Group 1[a] N=18			Group 2[a] N=18			Pooled N=36	
Parameter[a]	**Statistic**	**10 mg n=12**	**20 mg n=17**	**30 mg n=18**	**20 mg n=17**	**30 mg n=16**	**40 mg n=15**	**20 mg n=34**	**30 mg n=34**
C_{max}	Mean	18.3	38.9	62.6	36.3	56.0	78.2	37.6	59.5
(ng/mL)	SD	5.19	16.89	26.51	10.02	19.83	32.75	13.73	23.49
C_{min}	Mean	9.9	22.4	36.2	21.3	32.0	44.1	21.9	34.2
(ng/mL)	SD	3.70	11.6	20.4	7.28	16.0	21.6	9.53	18.3
$C_{ss,avg}$	Mean	14.0	31.6	49.8	29.5	45.7	61.5	30.5	47.8
(ng/mL)	SD	4.35	14.8	22.6	8.59	17.9	26.5	12.0	20.3
AUC_{0-12}	Mean	168.5	378.9	597.0	353.6	548.5	738.0	366.3	574.2
(ng·h/mL)	SD	52.25	177.46	271.63	103.08	214.69	317.41	143.38	244.06
T_{max}	Mean	4.8	5.0	4.8	4.6	4.6	5.1	4.8	4.7
(h)	SD	1.59	2.37	1.50	2.45	1.54	1.79	2.38	1.50
Peak-trough Fluctuation	Mean	62.2	54.9	57.0	52.1	55.1	58.7	53.5	56.1
(%)	SD	17.3	11.8	15.8	11.3	12.9	20.8	11.5	14.3

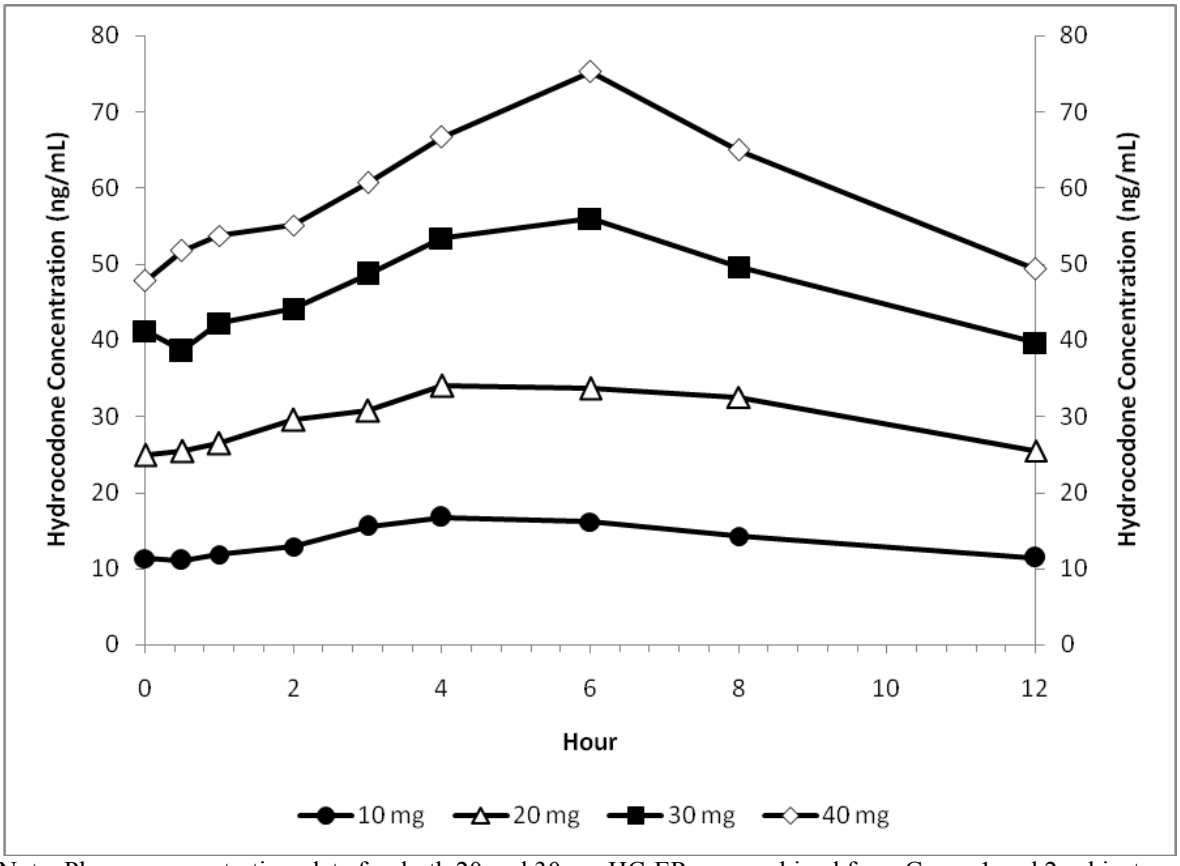
[a] Group 1 subjects with initial dose of 10 mg and Group 2 subjects with initial dose of 10 mg

Table 7: Assessment of Dose Proportionality, Study ELN154088-203

Parameter[a]	Statistic[b]	10 mg n=12	20 mg n=34[c]	30 mg n=34[d]
C_{max}	Ratio	1.02	0.945	0.994
	90% CI	0.904 – 1.16	0.864 – 1.03	0.909 – 1.09
AUC_{0-12}	Ratio	1.03	0.982	1.02
	90% CI	0.907 – 1.17	0.897 – 1.08	0.934 – 1.12

Source: ELN154088-203 CSR: Table 11.5.6.1.
[a] Parameters were dose-normalized for comparison
[b] Ratio and 90% CI were calculated relative to the 40 mg dose
[c] 17 subjects from Group 1 and 17 from Group 2
[d] 18 subjects from Group 1 and 16 from Group 2
CI = confidence interval.

Figure 3: Mean Plasma Hydrocodone Concentration-Time Profiles for HC-ER at Steady State (Study ELN-154088-203)

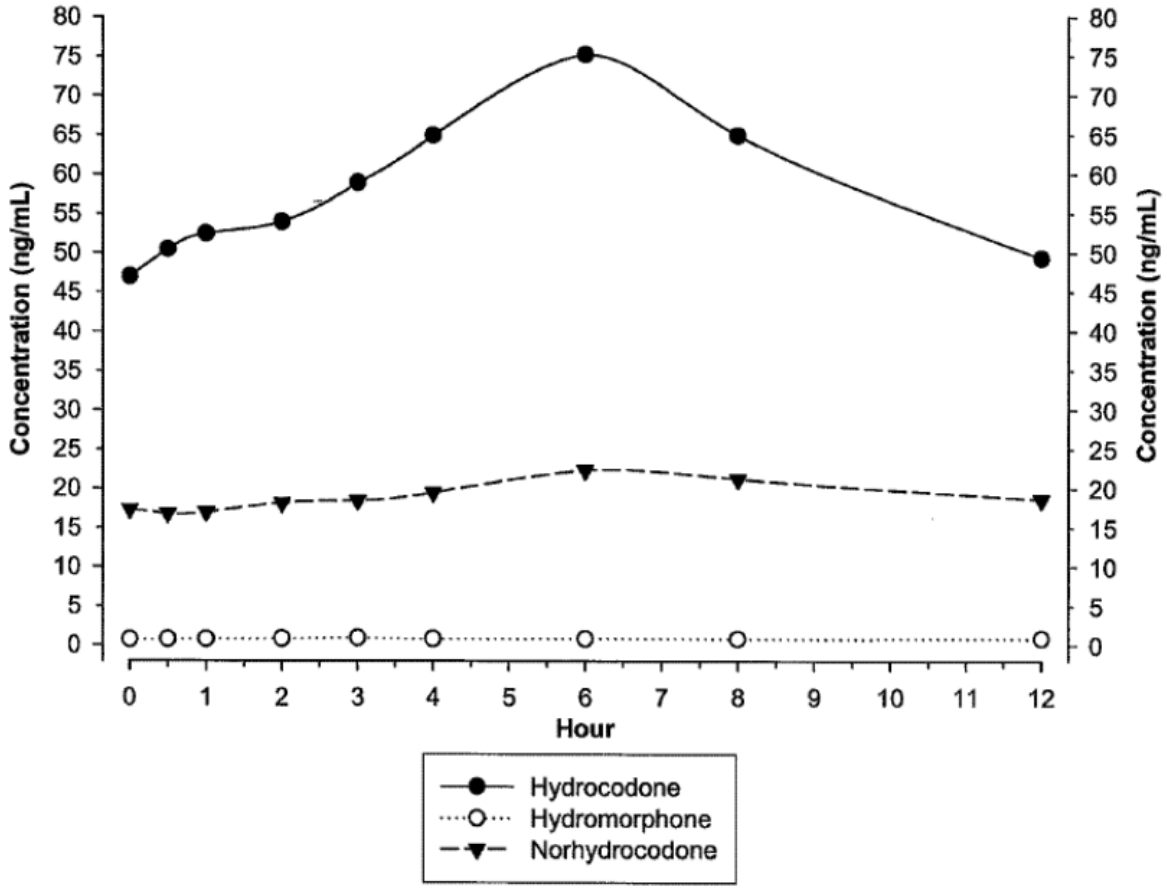


Note: Plasma concentration data for both 20 and 30 mg HC-ER are combined from Group 1 and 2 subjects. Group 1 subjects did not receive 40 mg HC-ER and Group 2 subjects did not receive 10 mg HC-ER. Profiles show plasma concentrations following the morning dose of 10, 20, 30 and 40 mg HC-ER after six previous days of q12h administration

4.2.3 Hydrocodone Metabolites

The metabolic pathway for hydrocodone in most species involves hepatic cytochrome P450 (CYP450) mediated biotransformation to norhydrocodone and hydromorphone (Otton 1993; Hutchinson 2004). The CYP3A4 isoenzyme catalyzes N-demethylation of hydrocodone to norhydrocodone and the CYP2D6 isoenzyme catalyzes O-demethylation of hydrocodone to hydromorphone. While hydromorphone is an active metabolite with substantially higher affinity for opioid receptors than hydrocodone, reductions in hydromorphone concentrations secondary to reduced CYP2D6 capacity (either due to drug-drug interactions or in phenotypic poor metabolizers) do not alter the clinical effects or abuse liability of hydrocodone (Kaplan 1997). Furthermore, all the clinical pharmacology studies conducted by Zogenix have consistently demonstrated that norhydrocodone is by far the most abundant metabolite (~35%) at levels that are significantly greater than hydromorphone (<2%). For example, the plasma concentrations of hydrocodone, hydromorphone and norhydrocodone as a function of time at steady state after administration of a 40 mg HC-ER are shown in Figure 4.

Figure 4: Mean Plasma Hydrocodone, Hydromorphone, and Norhydrocodone Concentration-Time Profiles at Steady State after Administration of 40 mg HC-ER (Study ELN-154088-203)



4.3 Effect of Food

Study ELN-0302002 evaluated the rate and extent of absorption of hydrocodone from HC-ER in both the fed and fasted states. The study was an open-label, two treatment, cross-over study in 12 healthy, adult subjects. Subjects were treated with a single oral dose of HC-ER 20 mg capsule either in the fed (high fat breakfast) and fasted states, with a 7 day washout between each dose. The plasma hydrocodone concentrations from this study are displayed graphically in Figure 5 and the PK parameters are shown in

Table 8. Comparable systemic absorption of single oral doses of 20 mg HC-ER was observed in both the fed and fasted states, as indicated by the similarity in AUC estimates and the 100% relative bioavailability. There was a slight increase in mean C_{max} under fed conditions (28.8 ng/mL compared to 22.7 ng/mL in the fasted state), which is likely related to delayed gastric emptying and absorption of the immediate release component of HC-ER in the presence of food. Based upon the lack of differences in $AUC_{0\text{-last}}$ and the relatively small differences in C_{max}, dosing of HC-ER is not restricted by the timing of meals.

Figure 5: Mean Plasma Hydrocodone Concentration-Time Profiles, Stratified by Fed Status (ELN-0302002)

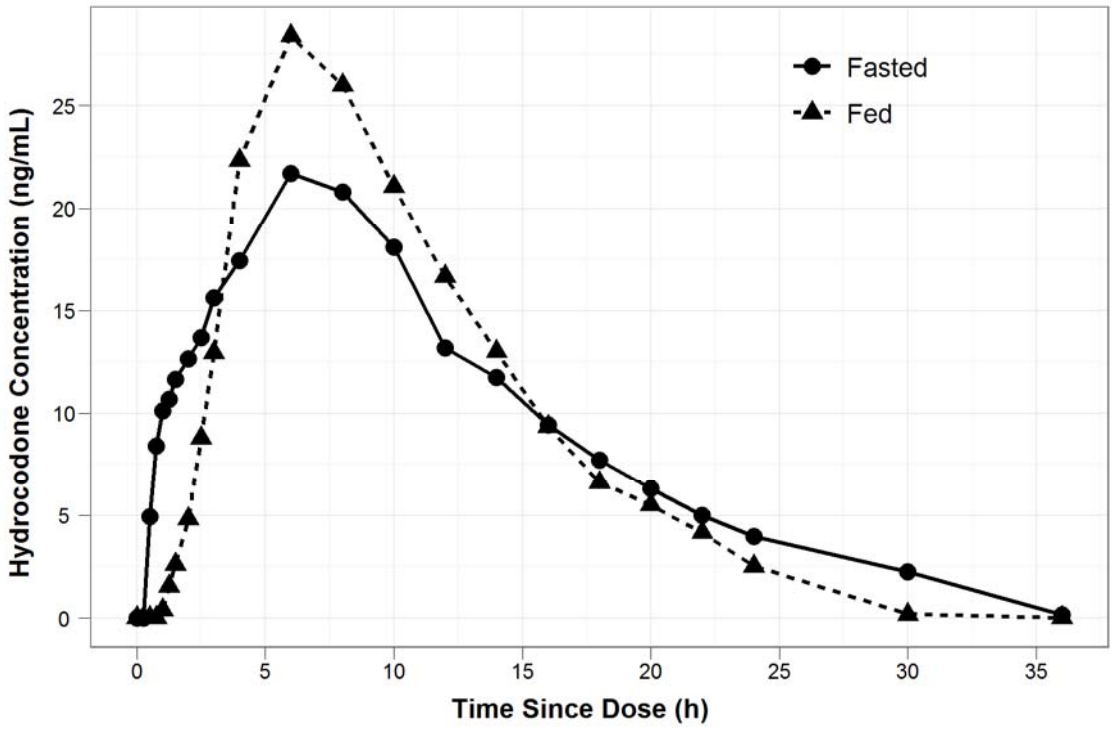


Table 8: Summary Statistics, Mean (%CV), for Hydrocodone PK Parameters - Study ELN-0302002

PK Parameter	Treatment A (Fasted) n=12	Treatment B (Fed) n=12
$AUC_{0\text{-}inf}$ (ng·h/mL)	345 (10.6)[a]	338 (16.3)
$AUC_{0\text{-}last}$ (ng·h/mL)	312 (14.6)	316 (17.0)
C_{max} (ng/mL)	22.7 (19.0)	28.8 (14.5)
t_{max}[b] (h)	8.00 (4.00 – 8.02)	6.01 (5.99 – 8.01)
$t_{1/2}$ (h)	6.48 (13.3)[c]	4.94 (21.7)
Relative Bioavailability[c]: $AUC_{0\text{-}inf}$ (%)	NA	100 (9.6)[c]
Relative Bioavailability[c]: $AUC_{0\text{-}last}$ (%)	NA	102 (11.5)

[a] n=11;
[b] Median (Min. – Max.) shown for t_{max};
[c] Reference was Treatment A

4.4 Effect of Alcohol

An alcohol effect is a common characteristic of ER opioid products. The effect of alcohol co-ingestion on the PK of HC-ER under fasted conditions was assessed in a three-treatment crossover study (Study ZX002-0901). Subjects who were under a naltrexone block were administered the highest HC-ER capsule strength (50 mg) with orange juice (0% alcohol) and 20% and 40% alcohol (a volume of 240 mL per administration). The top test condition of 240 mL of 40% alcohol is equivalent to 6 shots of 80-proof vodka on an empty stomach taken immediately with the HC-ER dose. Summary statistics for hydrocodone PK parameters, stratified by treatment, are provided in Table 9. This study showed that concomitant use of 20% alcohol and HC-ER did not result in any increase in systemic exposure or evidence of dose dumping relative to 0% alcohol. Conversely, the rate of absorption of hydrocodone from HC-ER was affected by 40% alcohol in the fasted state, as exhibited by an increase in C_{max} and a decrease in T_{max}. This most likely represents partial release of hydrocodone from the HC-ER micro-particles in the stomach by the 40% alcohol. A statistical comparison of the PK data (Table 10) showed HC-ER co-ingested with 20% and 40% alcohol were each bioequivalent based upon comparison of AUC to HC-ER administered in the absence of alcohol. HC-ER administered with 20% alcohol was also bioequivalent to HC-ER administered with no alcohol based upon comparison of C_{max}. However the 90% CIs for the C_{max} comparison of HC-ER co-ingested with 40% alcohol versus HC-ER administered with no alcohol was outside the accepted range for bioequivalence.

Table 9: PK Parameters for Hydrocodone Administered with and without Co-ingestion of alcohol - Study ZX002-0901

	Treatment		
Pharmacokinetic Parameters	**HC-CR + 0% Alcohol N=30**	**HC-CR + 20% Alcohol N=29**	**HC-CR + 40% Alcohol N=30**
Evaluable Subjects	29	28	21
C_{max} (ng/mL)			
Mean (%CV)	46.3 (18.6)	51.8 (20.7)	104 (42.0)
Min-Max	32.6 - 61.0	33.9 - 78.8	8.18 - 196
T_{max} (hr)			
Median	6.00	6.00	2.50
Min-Max	0.750 - 12.0	0.750 - 8.00	1.00 - 6.00
$AUC_{0\text{-last}}$ (ng . hr/mL)			
Mean (%CV)	832 (26.0)	878 (26.3)	963 (30.2)
Min-Max	452 - 1190	512 - 1356	65.1 - 1456
$AUC_{0\text{-inf}}$ (ng . hr/mL)			
Mean	846 (26.5)	900 (27.0)	972 (30.5)
Min-Max	454 - 1217	520 - 1368	67.4 - 1491
$t_{1/2}$ (hr)			
Mean	7.16 (16.5)	7.38 (18.3)	6.69 (16.9)
Min-Max	5.34 - 9.46	5.16 - 10.3	4.78 - 9.69

Table 10: Statistical Analysis of PK Data - Study ZX002-0901, (Primary Analysis)

	Treatments[a] and Comparisons	
PK Parameters	**Treatment A vs. C[b] (90% CI)[c]**	**Treatment B vs. C[b] (90% CI)[c]**
C_{max} (ng/mL)	202% (171, 240)	112% (95.9, 130)
$AUC_{0\text{-last}}$ (ng·hr/mL)	107% (91.2, 125)	105% (91.7, 121)
$AUC_{0\text{-inf}}$ (ng·hr/mL)	106% (90.9, 124)	106% (92.4, 122)

[a] Treatment A was HC-ER + 40% alcohol, Treatment B was HC-ER + 20% alcohol, and Treatment C was HC-ER + 0% alcohol.
[b] Treatment C (HC-ER + 0% alcohol) was the reference treatment used for comparison with Treatment A and Treatment B.
[c] CI: Confidence Interval: Ratio of parameter means for natural log transformed parameter (expressed as a percent).

A comparison of the HC-ER alcohol interaction data with those for other marketed ER opioid products is shown in Table 11. For HC-ER, the overall mean C_{max} ratio and maximum increase observed for in any individual for 40% alcohol versus 0% alcohol treatments is within the range of responses observed for other currently marketed ER opioid products (Embeda package insert; Johnson et al., 2008; Nucynta ER package insert; Opana ER package insert). The draft product insert for Zohydro ER states, "Patients must not consume alcoholic beverages, or prescription or nonprescription medications containing alcohol, while

on Zohydro ER therapy. The co-ingestion of alcohol with Zohydro ER may result in a potentially fatal overdose of HC".

Table 11: C_{max} Ratio of Opioids Administered with Co-ingestion of Alcohol

Product	Mean increase in C_{max} ratio relative to drug co-ingested with 0% alcohol		Maximum individual C_{max} ratio with 40% alcohol
	20% alcohol	40% alcohol	
Exalgo	1.35	1.37	2.51
Opana ER	1.31	1.70	2.70
Zohydro ER	1.1	2.0	4.0
Nucynta ER (100 mg)	–	1.48	4.38
Nucynta ER (250 mg)	–	1.28	2.67
Embeda	–	2.0	5.0
Kadian	–	1.0[a]	4.54

[a] Median
Sources: Embeda package insert; Johnson et al., 2008; Nucynta ER package insert; Opana ER package insert; Exalgo FDA slides.

4.5 Effects of Other Factors on Pharmacokinetics

4.5.1 Renal Impairment

Data from a study involving 28 subjects with varying degrees of renal impairment, matched using age and body mass index (BMI) to 9 subjects with normal renal function, showed that plasma hydrocodone concentrations were higher in subjects with renal impairment (Study ZX002-1002). C_{max} values were 15%, 48%, and 41% higher and AUC values were 15%, 57% and 44% higher in subjects with mild (creatinine clearance of 50 to 80 mL/min), moderate (30 to 50 mL/min) and severe (<30 mL/min) renal impairment, respectively. On the basis of these findings, no routine dose adjustment appears necessary in patients with renal impairment. However, since hydrocodone plasma levels may be increased in individuals with moderate to severe renal impairment, patients in this population should be monitored closely. The draft product insert for HC-ER states, "Patients with renal impairment may have higher plasma concentrations than those with normal function. No dosage adjustment is required but patients with renal impairment should be monitored closely."

4.5.2 Hepatic Impairment

Data from a study involving 20 subjects with mild-to-moderate hepatic impairment, matched using age and BMI to 10 subjects with normal hepatic function, showed that plasma concentrations were slightly higher in subjects with hepatic impairment (Study ZX002-1001). C_{max} values were 8% and 10% higher in subjects with mild and moderate hepatic impairment, respectively, while AUC values were 10% and 26% higher in subjects with mild and moderate hepatic impairment, respectively. On the basis of these findings, no routine dose adjustment appears necessary in patients with hepatic impairment. However, since hydrocodone plasma levels may be increased in some individuals with hepatic impairment, patients in this population should be monitored closely. The draft product insert for HC-ER states, "Patients with hepatic impairment may have slightly higher plasma concentrations

than those with normal function. No dosage adjustment is required but patients with hepatic impairment should be monitored closely."

4.5.3 Population Pharmacokinetics

A population PK analysis was conducted using the PK data from the HC-ER development program. The purpose of the analysis was to develop a population PK model to describe the PK of hydrocodone following administration of HC-ER and to determine if the PK was dose proportional over the entire dose range (10 – 50 mg). A covariate analysis was also undertaken to define those subject characteristics associated with the inter individual variability in hydrocodone PK. The full PK dataset contained 4,714 hydrocodone concentrations from 220 subjects. Using NONMEM (Version 7 release 1.2), a robust fit to the data was obtained using a two compartment model with linear elimination and a complex absorption component. The only significant covariate relationships were between creatinine clearance and hydrocodone clearance and between body surface area and hydrocodone volume of distribution. Once these relationships were incorporated into the model, there was no impact of dose, age, or sex on the PK of HC. The fact that a linear model for hydrocodone elimination provided an adequate fit to the observed data supports that HC-ER exhibits dose proportionality across all of the proposed dosage strengths (10-50 mg).

5 CLINICAL DEVELOPMENT

5.1 Overview of Clinical Program

The studies summarized in this section demonstrate that hydrocodone is safe and effective for the intended indication, management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

The overall clinical program consisted of ten studies in a total of 1568 subjects including subjects with chronic pain, healthy volunteers, subjects with renal and hepatic impairment, and subjects with acute pain. The clinical studies are summarized in Table 12. Study ZX002-0801 (Study 801) is the pivotal efficacy study for the NDA. Zogenix and the Agency agreed that a single pivotal study was appropriate for the chronic pain indication. Study ZX002-0802 (Study 802) provides long-term open-label safety data in a broad chronic pain population. Study 801 is discussed in detail in Section 5.2 and Study 802 is described in detail in Section 5.3. An integrated summary of safety for chronic pain studies is provided in Section 5.4 including an analysis of AEs by dose. A large Phase 2 study was performed in bunionectomy patients (Study ELN-154088-201). Zogenix chose to focus on a chronic pain indication and did not perform other acute pain studies. Safety results for bunionectomy study ELN-154088-201 are summarized in Section 5.4.5.

Table 12: HC-ER Clinical Studies (Phase 1- 3)

Study No.	Type of Study
PHASE 1 STUDIES	
ELN-0901001	Bioavailability of 20 mg Hydrocodone from Hydrocodone bitartrate formulation relative to Vicodin HP tablets in 18 healthy volunteers
ZX002-1102	Bioequivalence of 30 mg HC-ER formulation relative to Vicoprofen
ELN-0302002	Pharmacokinetics of 20 mg HC-ER formulation administered with and without food in 12 healthy volunteers
ZX002-0901	Bioavailability, safety and pharmacokinetics of 50 mg HC-ER formulation with 0%, 20%, 40% alcohol without food in 30 healthy volunteers
ZX002-1001	Pharmacokinetics and safety of 20 mg HC-ER formulation in 30 subjects with hepatic insufficiency
ZX002-1002	Pharmacokinetics and safety of 20 mg HC-ER formulation in 37 subjects with renal insufficiency
PHASE 2 STUDIES	
ELN-154088-201	Pharmacokinetics, safety and efficacy of 10 to 40 mg HC-ER in 241 subjects following bunionectomy surgery
ELN-154088-203	Multiple-dose pharmacokinetics and safety of HC-ER in 37 subjects with chronic osteoarthritis pain
PHASE 3 STUDIES	
ZX002-0801	Pivotal double-blind, placebo-controlled enriched enrollment randomized withdrawal efficacy and safety study of HC-ER in 510 subjects with chronic low back pain
ZX002-0802	Enriched enrollment open-label safety study of HC-ER in 638 subjects with chronic pain

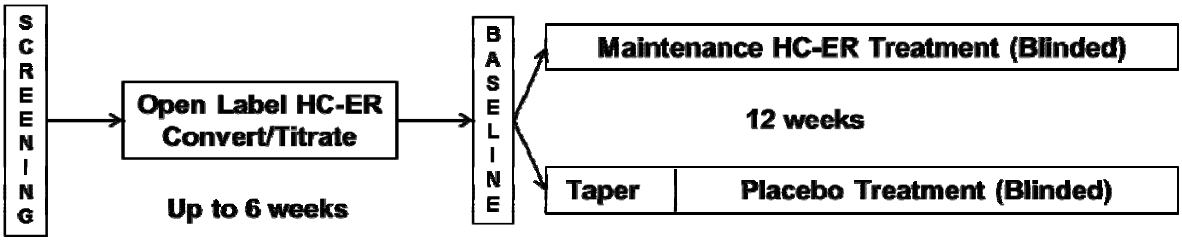
5.2 Pivotal Efficacy and Safety Study 801

5.2.1 Study Design – Study 801

Study 801 was a multicenter, double-blind, placebo-controlled study that used an enriched enrollment randomized withdrawal design (EERW), agreed between Zogenix and the Agency as an appropriate and validated approach to studying the efficacy of an ER opioid. Pivotal studies of most recently approved ER-opioid products used this design (e.g. Opana ER, Embeda, Exalgo, and Nucynta ER). An EERW study is different from many placebo-controlled studies, in that enrichment for drug-responsive patients occurs during an open-label run-in period, and then the primary endpoint is loss of pain control when responders are randomized to placebo or active drug. FDA refers to this as predictive enrichment (Temple, 2012).

Study 801 consisted of three distinct periods (Figure 6).

Figure 6: Study Design – Study 801



- Screening to determine eligibility to enter the study.
- Open-label conversion/titration phase (up to 6 weeks), where subjects were converted from their previous opioid therapy to HC-ER and then had their HC-ER dose titrated based on pain relief and tolerance to obtain an individual stabilized dose.
- Randomization (Baseline) to treatment with blinded study drug, either HC-ER or placebo, for a 12-week placebo-controlled maintenance treatment phase.

5.2.1.1 Screening, Inclusion/Exclusion

At Screening, subjects were eligible to enter the study if they: had a clinical diagnosis of moderate to severe CLBP present for at least several hours a day for a minimum of 3 months; were classified as non-neuropathic (Class 1 and 2), neuropathic (Class 3, 4, 5, and 6), or symptomatic for more than 6 months after low back pain surgery (Class 9) based on the Quebec Task Force Classification of Spinal Disorders; required around-the-clock opioid therapy; were taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 45 mg oral morphine equivalents per day (as any immediate or ER opioids); had an average clinic pain score ≥4 on the 11-point (0-10) Numerical Rating Scale (NRS) for the last 24 hours of the Screening Phase; had stable adjunctive regimens (e.g., physical therapy, biofeedback therapy); were in generally good health; were able to effectively communicate with the study staff and able to complete study procedures; and voluntarily provided written informed consent.

Subjects were excluded from entering the study if they: had any condition that would increase the risk of opioid-related AEs (e.g. chronic carbon dioxide retention, respiratory depression, chronic constipation, gastroparesis, inflammatory bowel disease, active seizure disorder); had a history of any illicit substance or alcohol abuse in the past 5 years or any history of opioid abuse; had a positive urine drug screen for illicit drugs, or non-prescribed controlled substances; had a Hospital Anxiety and Depression Scale (HADS) index score of >12 in either depression or anxiety subscales or an established history of major depressive disorder that was poorly controlled with medication; had an active diagnosis of fibromyalgia, complex regional pain syndrome, neurogenic claudication due to spinal stenosis, spinal cord compression, acute nerve root compression, severe or progressive lower extremity weakness or numbness, bowel or bladder dysfunction as a result of cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain because of secondary infection or tumor, or pain caused by a confirmed or suspected neoplasm; had a surgical procedure for back pain within

6 months, a nerve or plexus block within 1 month, or botulinum toxin injection in the lower back region within 3 months; had any other chronic pain condition that would interfere with the assessment of low back pain (e.g., OA, rheumatoid arthritis, post-herpetic neuralgia, pain associated with diabetic neuropathy, migraine headaches requiring opioid therapy); had uncontrolled hypertension; had a BMI >45 kg/m^2; had a clinically significant abnormality in clinical chemistry, hematology or urinalysis; had an active or pending workman's compensation or litigation related to back pain; had a known allergy or hypersensitivity to opioids; had a history of clinically significant intolerance to hydrocodone; had a history of intolerance to acetaminophen; had taken any investigational drug within 30 days prior to the Screening visit; was currently enrolled in another investigational drug study; or had used a monoamine oxidase inhibitor within 14 days.

5.2.1.2 Open-Label Conversion/Titration Phase

During the open-label conversion/titration phase, subjects were initially converted to a dosage of HC-ER that was approximately 20%-30% less than the conversion dose of HC-ER calculated based on their prior opioid treatment. After conversion, if the subject did not achieve satisfactory analgesia with the initial dose, the subject was titrated, in an open-label fashion to their individual optimum HC-ER dose. Rescue medication (hydrocodone 5 mg/acetaminophen 500 mg) was supplied by Zogenix, and up to 4 tablets per day were permitted as supplemental pain medication due to inadequate pain relief. A stabilized dose was one that subjects tolerated well for at least 7 days with an average 24-hour daily average pain score of ≤4 on the NRS during the last 7 days prior to Baseline, a reduction of 2 points on the NRS compared to Screening, and no more than 2 tablets of rescue medication on any day. Subjects who did not achieve a stabilized dose, who did not tolerate HC-ER treatment due to AEs, who were not compliant with dosing or drug accountability, or who could not complete required study procedures (e.g. study visits, use of the electronic diary) were discontinued from the study.

5.2.1.3 Randomization

Subjects were eligible to be randomized if they: had been stabilized on at least 40 mg per day but not more than 200 mg per day of HC-ER; had reached a stabilized dose within 6 weeks of starting open-label treatment; had a reduction of 2 points on the NRS in the average pain intensity over the last 7 days prior to randomization compared to the Screening score; had tolerable side effects; were willing to stay on the medication for the duration of the study; had been compliant with diary completion and drug accountability procedures; and had an average 24-hour daily average pain score of ≤4 on the NRS during the last 7 days prior to randomization. The time of randomization was considered as Baseline.

5.2.1.4 Maintenance Treatment Phase

During the maintenance treatment phase, subjects were randomized 1:1 to receive either the respective stabilized dosage of HC-ER or placebo, taken orally every 12 hours. The dosage could not be adjusted during the 12 weeks of maintenance treatment. Blinded study drug was supplied in blister packs, containing either HC-ER supplied as 10, 20, 30, 40, or 50 mg capsules, or matching placebo. The initial 14-day blister pack contained a tapering dose of

HC-ER for subjects randomized to placebo, and a mock taper for subjects randomized to receive HC-ER. Rescue medication (hydrocodone 5 mg/APAP 500 mg) was supplied by Zogenix, and up to 2 tablets per day were permitted as supplemental pain medication. All other opioid medications were prohibited, along with non-steroidal anti-inflammatory drugs including aspirin (except for cardiovascular prophylaxis), monoamine oxidase inhibitors, and any other investigational drug. Central nervous system (CNS) depressants, muscle relaxants, sedative, antidepressants, anticonvulsants, benzodiazepines, inhaled steroids, physical therapy, biofeedback therapy, acupuncture therapy, and herbal remedies could not be started during the study, but a stable pre-study regimen could be continued.

5.2.1.5 Endpoints and Sample Size

The primary efficacy endpoint of the study was the change from Baseline (randomization) to the end of the double-blind maintenance treatment phase (Day 85 or last visit) in average pain intensity on the 11-point NRS as recorded daily in an electronic diary, comparing HC-ER with placebo. Prospectively identified key secondary efficacy endpoints were response rate (with response defined as a 30% improvement from the screening pain intensity score to the Day 85 pain intensity score), and satisfaction with pain medication (measured by the Subject Global Assessment of Medication, SGAM). The key secondary endpoints were analyzed according to a hierarchical (gatekeeping) testing procedure. Thus, a key secondary endpoint was only to be analyzed if the result of the preceding primary or key secondary endpoint was statistically significant in favor of HC-ER. The scales used for the primary and key secondary endpoints are shown in Appendix 1.

Based on other EERW studies of ER opioids, it was estimated that a sample size of 150 subjects per group (300 randomized subjects total) would provide 91% power to detect a treatment difference of 1.0, assuming a standard deviation of 2.6 per group. It was anticipated that the magnitude of the difference in average daily pain intensity scores between the HC-ER group and the placebo group would be modest, because placebo-treated subjects would not be likely to allow their pain to return to pre-treatment levels, and would go off study and seek alternative pain management once a small increase in pain was experienced.

5.2.2 Demographics – Study 801

The study was conducted at 57 sites across all regions of the continental US between March 2010 and July 2011. The demographic characteristics of the 510 subjects who were enrolled in the study and were treated with HC-ER in the conversion/titration phase of the study are shown in Table 13. The mean age of enrolled subjects was 49 years, the majority were female (54%) and White (79%). The mean pain score (daily average NRS pain intensity score) at enrollment was in the severe range at 7.0 out of 10. The median pain score was also 7.0, so half of the enrolled subjects had average daily pain scores above 7 out of ten. The average disability score, Oswestry Disability Inventory (ODI), was only calculated for the subjects that were randomized to enter maintenance treatment, and was 62.1 (HC-ER group) and 62.3 (Placebo group) out of 100 (range 32-96), which indicates severe and debilitating back pain in the enrolled population. To place this result in context, the ODI of adults without any significant medical condition averaged 10 out of 100, and for patients with metastatic cancer the average ODI was 48 out of 100 (Fairbank 2000). At study entry, subjects were taking an average of 83.8 mg of morphine equivalents/day (range 34 – 415 mg), with a wide variety of agents used, including two or more opioids in many cases. Despite this, their pain management regimens were evidently not providing adequate pain relief or preventing disability from chronic pain as indicated by the high Screening NRS pain and ODI disability values.

The demographic characteristics of the 302 subjects who were randomized to receive maintenance treatment with blinded study drug are also shown in Table 13 (subject disposition is discussed in Section 5.2.3). All Screening characteristics were similar between the group randomized to receive HC-ER and the group randomized to receive placebo except for sex, where there were was a preponderance of females in the HC-ER group. No evidence was found that this minor imbalance affected study outcomes (see Section 5.2.4.4). There were only slight differences between subjects who were randomized to receive maintenance treatment and those who were not, with the latter about 2 years younger, with more males and non-Whites, but with very similar Screening pain scores (data not shown).

Table 13: Demographic Characteristics for the Conversion/Titration and Maintenance/Treatment Phase, Study 801

	Conversion/Titration Phase	Maintenance Treatment Phase	
	(N=510)	HC-ER (N=151)	Placebo (N=151)
Age (years)			
Mean (SD)	49.4 (11.8)	50.4 (10.94)	50.8 (12.37)
Range	18-75	21 – 74	24 – 74
Sex			
Male	237 (46.5%)	58 (38.4%)	77 (51.0%)
Female	273 (53.5%)	93 (61.6%)	74 (49.0%)
Race			
White	404 (79.2%)	123 (81.5%)	120 (79.5%)
Black or African American	91 (17.8%)	26 (17.2%)	25 (16.6%)
Other	15 (2.9%)	2 (1.3%)	6 (4.0%)
BMI (kg/m^2)			
Mean (SD)	30.4 (6.4)	31.3 (6.3)	30.2 (6.3)
Range	26-48	20-44	18-44
Average Pain Score at Screening (Before Titration)			
Mean (SD)	7.0 (1.39)	6.9 (1.5)	6.9 (1.4)
Range	4 - 10	4 – 10	4 – 10
Prestudy Opioid Usage (mg/day MS equivalents)			
Mean (SD)	83.8 (54.1)	76.8 (47.8)	79.2 (46.5)
Range	34 - 415	34 - 300	34 - 330
Oswestry Disability Index at Screening			
Mean (SD)	50.0 (13.2)	48.9 (13.5)	51.0 (13.3)
Range	19-88	22-80	22-86
Baseline Average Pain Score (After Titration)			
Mean (SD)	-	3.1 (0.9)	3.1 (1.0)
Range	-	0 – 6	0 – 7

Following their treatment with open-label HC-ER in the conversion/titration phase, the average NRS pain scores were reduced at the time of randomization to 3.1 for the group subsequently randomized to HC-ER and 3.1 for the group subsequently randomized to placebo (from 7.0 at study entry, respectively). This represents a substantial and clinically important reduction in average pain score of 4 NRS units out of 10.

5.2.3 Subject Disposition – Study 801

5.2.3.1 Conversion/Titration Phase

510 subjects with CLBP were enrolled in Study 801. A total of 208 subjects (41%) discontinued during open-label treatment with HC-ER in the conversion/titration phase (Table 14). The most common reason for discontinuation was 'Protocol specified criteria', which included failure to reach a stabilized dose of HC-ER within 6 weeks of open-label treatment, failure to reach an absolute score of ≤4 or a 2-point reduction in the NRS pain scale, positive drug screen, or use of prohibited concomitant medication. The next most common reason for discontinuation from the conversion/titration phase was noncompliance,

which included failure to record daily pain scores and study drug accountability information in a portable electronic diary, excessive or inappropriate use of HC-ER or rescue medication, and drug accountability issues. Zogenix conducted this study under a particularly strict compliance program, with forced discontinuations for even minor protocol violations. As a result, discontinuations due to protocol specified criteria and noncompliance are relatively high in this study. One advantage of the EERW design is that the conversion/titration period allows the investigators to identify subjects who are not good candidates for study participation, for reasons such as poor study activity participation, or if they are found to demonstrate drug seeking behaviors.

5.2.3.2 Maintenance Treatment Phase

A total of 302 subjects (59%) were randomized into the double-blind maintenance treatment phase (151 to HC-ER and 151 to placebo). A total of 183 randomized subjects (124 in the HC-ER group and 59 in the placebo group) completed the study, while 119 subjects (27 in the HC-ER group and 92 in the placebo group) discontinued early. Reasons for discontinuation for the 119 subjects who discontinued early in the maintenance treatment phase are provided in Table 14. By far the most common reason for leaving the study during maintenance treatment was lack of efficacy, given as the primary reason for discontinuation by 42.4% of the placebo group, but only for 9.3% of the HC-ER group. Discontinuation for opioid withdrawal occurred in 4.6% of the placebo group but in no subjects in the HC-ER group. Discontinuations over time for lack of efficacy, AEs and all causes are shown graphically in Section 5.2.4.3.1.

Table 14: Reasons for Early Discontinuation, Study 801

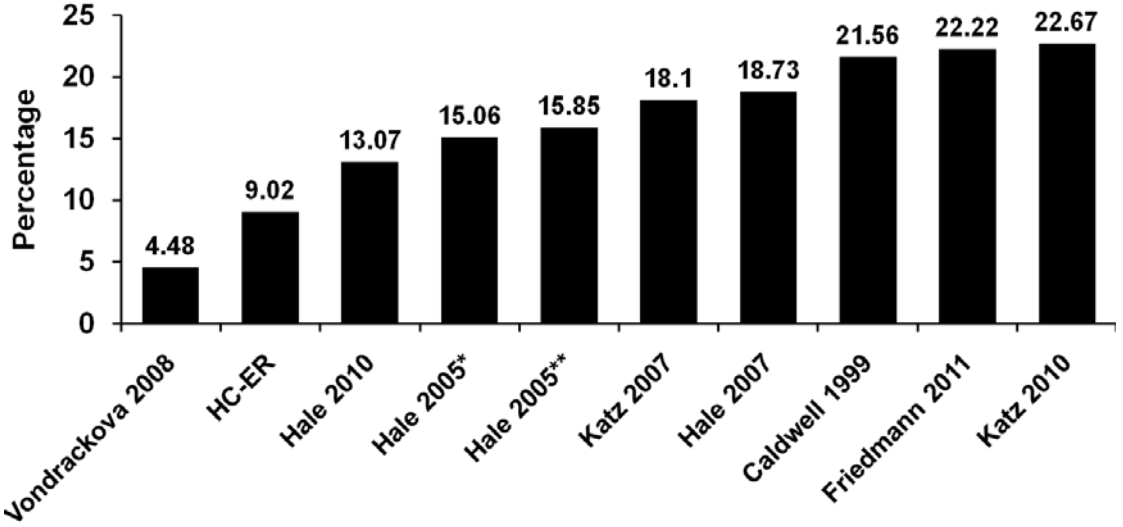
Reasons for Discontinuation	Conversion/Titration Phase (N=510)	Maintenance Treatment Phase	
		HC-ER (N=151)	Placebo (N=151)
Number of Subjects	208 (40.7%)	27 (17.9%)	92 (60.9%)
Protocol specified criteria	67 (13.1%)	1 (0.7%)	2 (1.3%)
Noncompliance	47 (9.2%)	4 (2.6%)	7 (4.6%)
Adverse event	46 (9.0%)	2 (1.3%)	5 (3.3%)
Withdrew consent	23 (4.5%)	5 (3.3%)	5 (3.3%)
Lack of efficacy	17 (3.3%)	14 (9.3%)	64 (42.4%)
Withdrawn by Investigator	2 (0.4%)	0 (0.0%)	1 (0.7%)
Opioid withdrawal	1 (0.2%)	0 (0.0%)	7 (4.6%)
Lost to follow-up	5 (1.0%)	1 (0.7%)	0
Other	0	0	1 (0.7%)

5.2.3.3 Meta-analysis of Discontinuations

A meta-analysis of EERW studies of extended- or controlled-release opioids was conducted. The goal was to find published articles of clinical studies that use an enriched enrollment, randomized withdrawal study design when evaluating a systemic (oral or transdermal) opioid for any type of chronic pain. Details of the analysis are shown in Appendix 2. Using the same meta-analysis methods that were applied to the efficacy results, discontinuation rates due to AEs and loss or lack of efficacy with HC-ER were evaluated in relation to those of other approved and market products. As shown in Figure 7, Figure 8, Figure 9, and Figure 10 rates of discontinuation due to AEs or loss of efficacy during the conversion/titration phase are

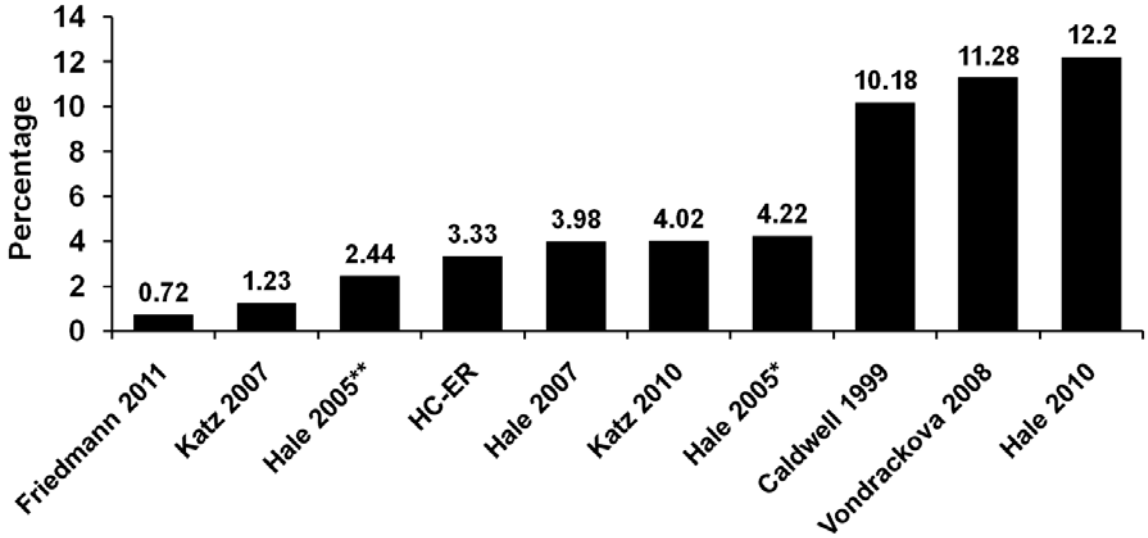
numerically lower than many other published studies of similarly designed EERW trials. Rates of discontinuation due to AEs or lack of efficacy in the double-blind phase are consistent with those reported with other approved and marketed ER/CR opioids. It should be noted that any observed differences may be due either to chance, or to differences in study design or conduct, and may not be attributable to any differences between the medications, but there is no indication that HC-ER resulted in greater numbers of discontinuation than the other published agents.

Figure 7: Discontinuations due to Adverse Events in the Titration Phase of EERW Studies of Oral Full Mu Agonists



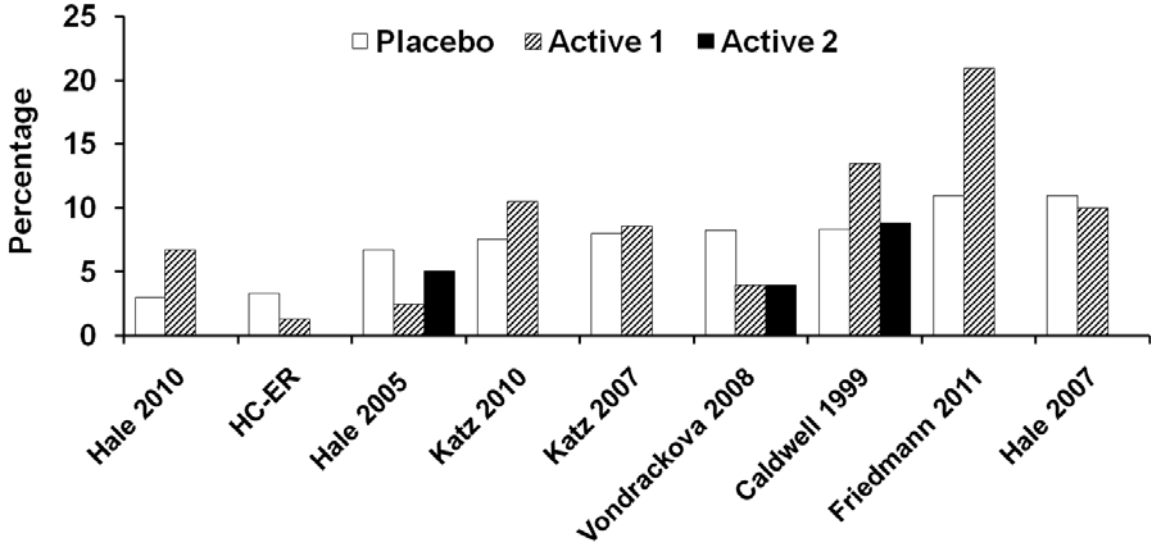
*Comparator 1 (oxymorphone ER) **Comparator 2 (oxycodone CR)
EERW = enriched enrollment randomized withdrawal.

Figure 8: Discontinuations due to Loss of Efficacy in the Titration Phase of EERW Studies of Oral Full Mu Agonists



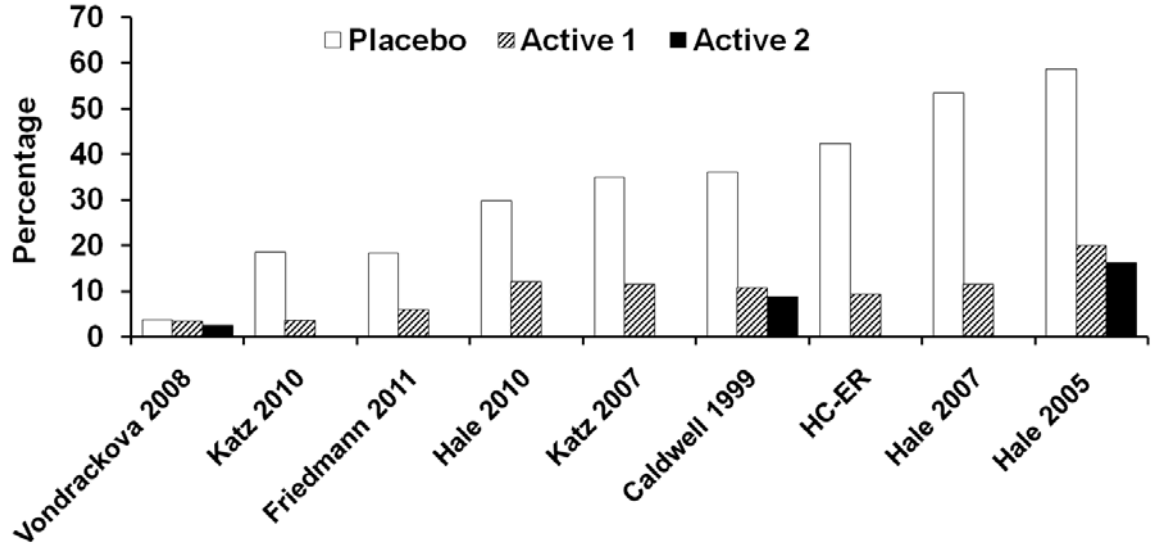
*Comparator 1 (oxymorphone ER) **Comparator 2 (oxycodone CR)
EERW = enriched enrollment randomized withdrawal.

Figure 9: Discontinuations due to Adverse Events in the Double-Blind Phase of EERW Studies of Oral Full Mu Agonists



All active arms were full mu agonists (oxycodone, oxymorphone, hydromorphone, or hydrocodone). Three studies (Vondrackova 2008; Caldwell 1999; Hale 2005) had 2 opioid arms.
EERW = enriched enrollment randomized withdrawal.

Figure 10: Discontinuations due to Lack of Efficacy in the Double-Blind Phase of EERW Studies of Oral Full Mu Agonists



All active arms were full mu agonists (oxycodone, oxymorphone, hydromorphone, or hydrocodone). Three studies (Vondrackova 2008; Caldwell 1999; Hale 2005) had 2 opioid arms.
EERW = enriched enrollment randomized withdrawal.

5.2.4 Efficacy Results – Study 801

The efficacy of HC-ER compared to placebo was robust across a variety of standard methods for examining pain intensity in clinical trials. There were statistically significant positive results for the primary analysis, as well as for both of the two prespecified key secondary analyses. Although not part of the prespecified hierarchical testing procedure, there were also statistically significant differences for nearly all of the other secondary endpoints. The results of these analyses are described in the following sections.

5.2.4.1 Primary Endpoint – Study 801

5.2.4.1.1 Primary Efficacy Analysis

The primary efficacy endpoint of Study 801 was the change from Baseline to the Day 85 visit in the average 24-hour pain intensity ratings on a 0-10 NRS (Appendix 1) from daily electronic diaries. Baseline was defined as the mean of the last 7 days on stabilized dosing of the average pain intensity rating prior to randomization into the maintenance treatment phase. The Day 85 visit was defined as the mean of the last 7 days of the average pain intensity rating prior to the Day 85 study visit of the treatment phase. If a subject had fewer than 7 scores in the last 7 days, the mean of the available scores was used.

The primary efficacy analysis population was the Intent-To-Treat (ITT Population), and all 302 randomized subjects were included in the analysis. Missing pain scores were imputed using methods agreed between Zogenix and the Agency: baseline observation carried forward for subjects who discontinued due to opioid withdrawal; screening observation carried forward for subjects who discontinued due to AEs; and last observation carried forward for subjects who discontinued due to lack of efficacy and other reasons.

The primary efficacy analysis was completed using an analysis of covariance (ANCOVA) model. The dependent variable was the change from baseline to Day 85. The model included treatment group as a factor and the baseline pain score and screening pain score as covariates. Based on this model, the HC-ER and placebo groups were compared using a 2-sided t-test at the 5% level of significance.

HC-ER was superior to placebo in the change from Baseline to the end of the study in average daily pain intensity score ($p=0.008$, Table 15), with a change of 0.5 units on the NRS pain scale for HC-ER treated subjects, and 1.0 units for placebo-treated subjects. Note that both groups experienced a large decrease in average daily pain intensity score of 4.0 units during their initial treatment with HC-ER during the conversion/titration phase of the study (Table 13). Additionally, subjects receiving HC-ER largely remained in the study, while more subjects in the placebo arm left the study early (Figure 16), with the primary reason for discontinuing being lack of efficacy (Table 14).

Table 15: Primary Efficacy Endpoint: Change from Baseline of Average Daily Pain Intensity Score (patient diary), ITT population, Study 801

Change from Baseline	HC-ER (N=151)	Placebo (N=151)
Mean (SD)	0.48 (1.563)	0.96 (1.550)
Range	-3.0 – 5.3	-2.4 – 6.7
LS Mean	0.48	0.95
p-value[a]	*0.008*	

[a] Treatment comparison using ANCOVA with treatment group as a fixed effect and screening pain score and baseline pain score as covariates.
ANCOVA = analysis of covariance.

5.2.4.1.2 Sensitivity Analyses of the Primary Endpoint

Post-hoc sensitivity analyses of the primary efficacy endpoint based on the use of the linear mixed model for repeated measurements were conducted. This analysis approach makes use of all available data from each subject, without imputation for missing values.

The dependent variable was the vector of changes in NRS pain score from Week 0 to each subsequent time point. Thus, there was a maximum of five observations per subject. The repeated measures model included fixed effects for treatment (two levels), time (five levels), and the interaction between treatment and time. In addition, the Screening and Baseline pain scores were included as covariates, in order to match the prespecified primary analysis approach. An unstructured covariance model was used to model the variances and covariances of the repeated measurements.

The comparisons of primary interest were the estimated differences between HC-ER and placebo at each of Weeks 1, 2, 4, 8, and 12. Table 16 summarizes the results of the repeated measures analysis model. The point estimate and standard error (SE) of the difference between HC-ER and placebo is displayed at each time point. In addition, the two sided p-value from the test of the null hypothesis that the mean difference is equal to zero is also displayed.

At each of the time points there was a significant reduction in pain score for HC-ER versus placebo ($p<0.001$), and the magnitude of the treatment difference tended to increase over time. At the primary time point (Week 12), the magnitude of the mean difference was approximately 1 point. Overall, the results of the analyses based on the linear mixed models for repeated measurements were consistent with the results of the prespecified primary efficacy analysis.

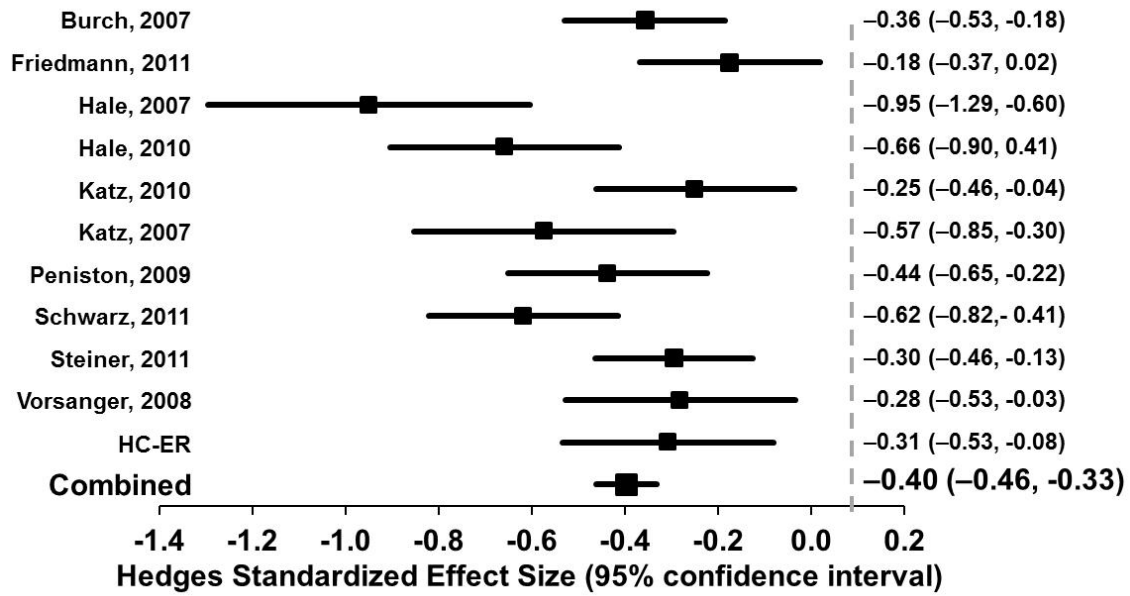
Table 16: Results of Linear Mixed Models Analysis of the Primary Endpoint

Time Point	Treatment Difference (HC-ER – Placebo)	SE	p-value
Week 1	-0.38	0.10	< 0.001
Week 2	-0.59	0.14	< 0.001
Week 4	-0.81	0.17	< 0.001
Week 8	-0.77	0.19	< 0.001
Week 12	-0.99	0.23	< 0.001

5.2.4.1.3 Meta-Analyses of the Primary Endpoint

A meta-analysis of EERW studies of extended- or controlled-release opioids was conducted. The goal was to find published articles of clinical studies that use an enriched enrollment, randomized withdrawal study design when evaluating a systemic (oral or transdermal) opioid for any type of chronic pain. Details of the analysis are shown in Appendix 2. As shown in Figure 11, this meta-analysis demonstrated that the effect of HC-ER net of placebo (expressed as a standardized effect size, [SES]) is within the range of effect sizes found in similarly designed studies of other ER opioids. Direct comparisons of SES across studies cannot be made, as numerous factors can affect observed effect size, such as trial structure, dosing approach, concomitant analgesic, use of rescue medications, primary endpoint used, number of patients and sites, geography, and year of conduct. However the meta-analysis presented here shows that the SES of HC-ER is within expected norms.

Figure 11: Meta-analysis: Standardized Effect Size for EERW Trials in Chronic Pain (Change in PI from randomization until week 12)



EERW = enriched enrollment randomized withdrawal.

5.2.4.2 Key Secondary Endpoints

When evaluating clinical data of any new therapy, group differences must be evaluated in light of measures of individual improvement. As many therapies benefit subgroups of patients in different ways, it is critical to understand whether a small between-group effect is masking a significant benefit to a subset of the patient population. For this reason, responder analyses are often employed to assess individual improvement. As stated by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), "identifying which patients can be considered responders is often a critical aspect of interpreting clinical trial results. Responder analyses make it possible to compare the percentages of patients who achieve meaningful outcomes between treatment and control groups or between different treatment conditions, a readily interpretable approach to presenting clinical trial outcomes" (Dworkin 2009).

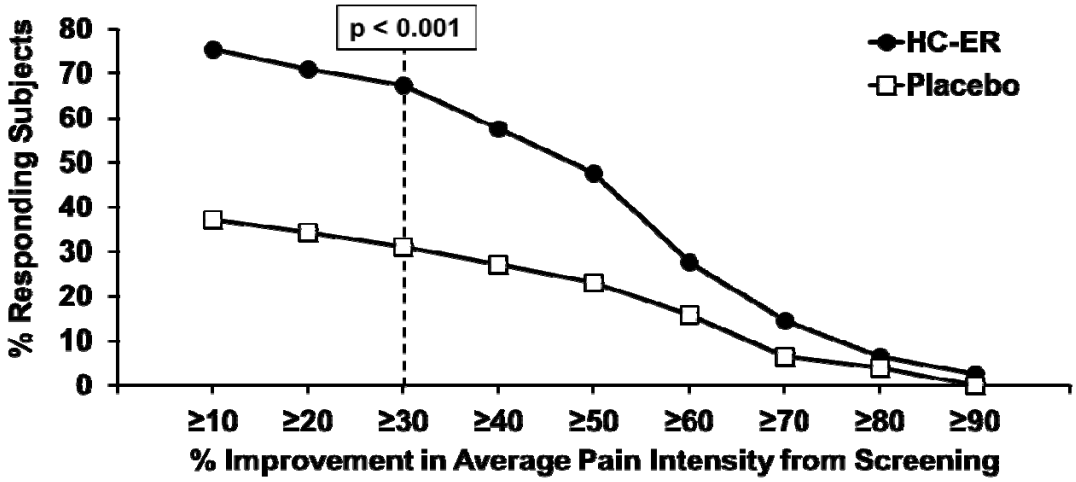
5.2.4.2.1 Responder Analysis – Study 801

A responder analysis was one of two pre-specified key secondary endpoints of the study, and was to be conducted only if the primary efficacy analysis of the study was statistically significant. Response was defined based on the percent improvement in average pain intensity as measured daily by the 0-10 NRS from the Screening 24-hour average pain intensity score to the Day 85 pain score (mean of the last 7 days prior to the Day 85 study visit). A responder was defined as a randomized subject who completed the 12-week maintenance treatment period and who experienced at least a 30% improvement in the pain intensity score. Subjects with missing data at Day 85 or who terminated early from the study were considered non-responders. The proportion of responders was summarized for each treatment group and compared using Pearson's chi-square test.

For this key secondary endpoint, there were 102 subjects (68%) classified as responders in the HC-ER group, compared with 47 subjects (31%) in the placebo group. This difference was statistically significant ($p<0.001$), with a much larger proportion of subjects who responded to treatment in the HC-ER group than in the placebo group. Although it was not a prespecified secondary endpoint, considering a 50% response, there were 72 subjects (48%) classified as responders in the HC-ER group, compared with 35 subjects (23%) in the placebo group ($p<0.001$). These results are clinically meaningful, as a 30% response is considered moderately important, and a 50% response is considered substantial (Dworkin 2005).

A standard display of responder rates using multiple percentage of improvement cutpoints from 10%-90% is shown in Figure 12. The proportion of subjects with improved pain intensity was consistently higher across all response rate levels for the HC-ER group compared to the placebo group.

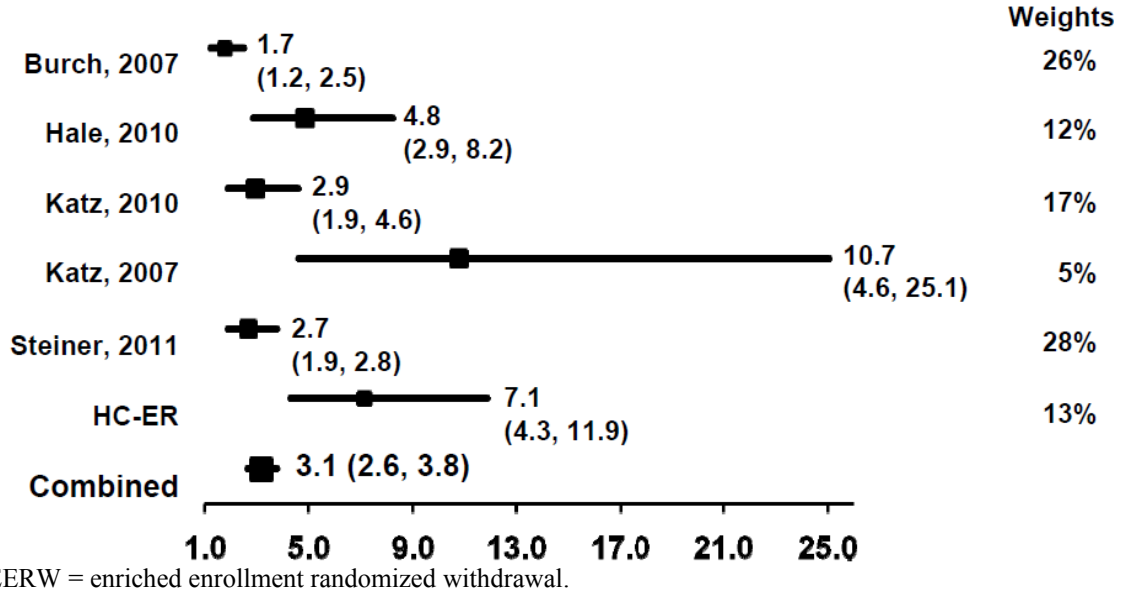
Figure 12: Response Rate − ITT Population, Study 801



5.2.4.2.2 Meta-Analysis of Responder Rates

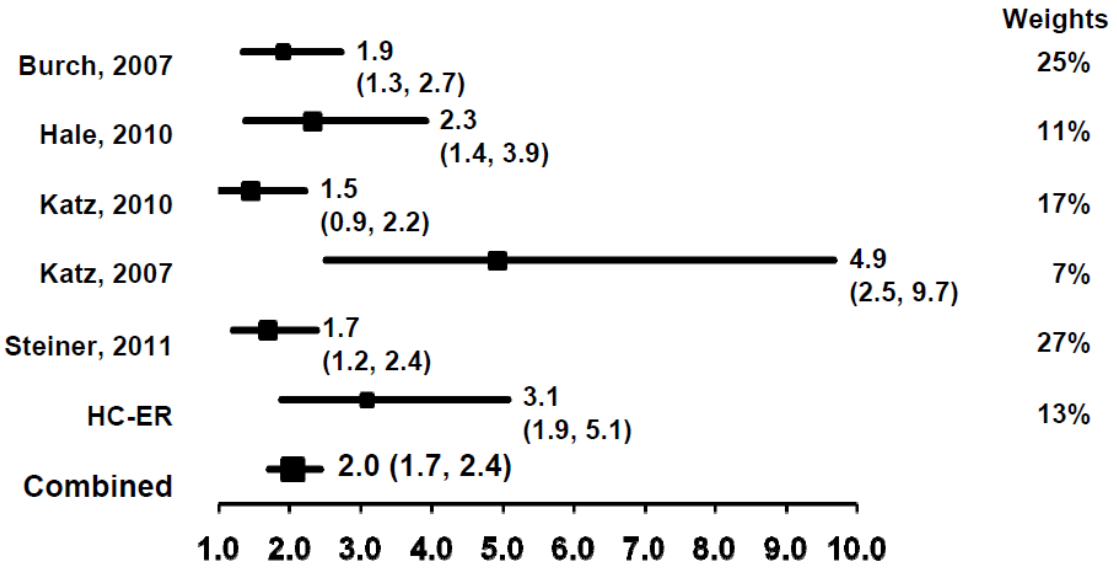
Responder rates were also examined using meta-analysis (Appendix 2). As shown in Figure 13 and Figure 14, this meta-analysis demonstrated that the effect of HC-ER net of placebo (expressed as an odds ratio) is within the range of effect sizes found in similarly designed studies of other ER opioids. Direct comparisons of SES across studies cannot be made, as numerous factors can affect observed effect size, such as trial structure, dosing approach, concomitant analgesic, use of rescue medications, primary endpoint used, number of patients and sites, geography, and year of conduct. However, the meta-analysis presented here shows that the response rate of HC-ER is within expected norms.

Figure 13: Meta-Analysis: 30% Responders at Week 12 for EERW Trials in Chronic Pain (Odds Ratio, Change in PI from randomization until week 12, n=6)



EERW = enriched enrollment randomized withdrawal.

Figure 14: Meta-Analysis: 50% Responders at Week 12 for EERW Trials in Chronic Pain (Odds Ratio, Change in PI from randomization until week 12, n=6)



EERW = enriched enrollment randomized withdrawal.

5.2.4.2.3 Patient Satisfaction – Study 801

An assessment of patient satisfaction with pain medication was the second of two pre-specified secondary endpoints, and was only to be conducted if both the primary efficacy endpoint and the analysis of the key secondary responder endpoint were statistically significant in favor of HC-ER. Using a validated patient global assessment of medication (SGAM, Appendix 1), subjects were asked, "How satisfied are you with your pain medicine?" The nominal response categories of "not at all", "a little bit", "moderately", "very much", and "completely" were scored as 1, 2, 3, 4, and 5, respectively. A higher score indicates that the subject was more satisfied with study drug than with their pre-study pain medication(s). SGAM scores were collected at Screening, Baseline, and Day 85 of the study. Change from screening to Day 85 in SGAM was analyzed using a t-test from an ANCOVA model with treatment group as a fixed factor, and screening assessment score as a covariate.

As shown in Table 17, the mean change from Screening to Day 85 in SGAM score was 0.8 units for the HC-ER group, compared with 0.0 units for the placebo group. This difference between treatment groups was statistically significant ($p<0.001$), indicating a greater degree of satisfaction with HC-ER than with placebo.

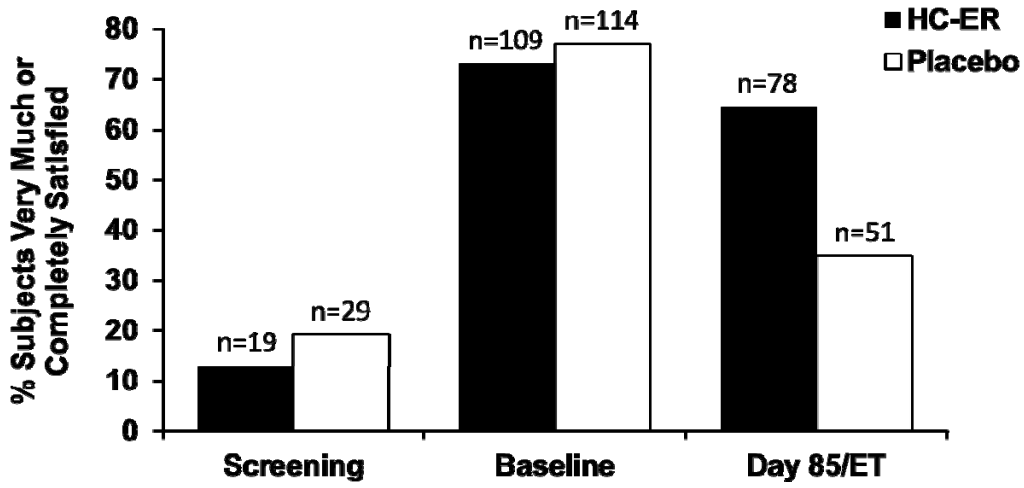
An additional post hoc analysis of the SGAM was based on the proportion of subjects very much or completely satisfied with their pain medication. These results are displayed in Figure 15. As expected, only a very small proportion of subjects (16%) were very much or completely satisfied with their pain medication when they entered the study, prior to receiving HC-ER. At the time of randomization, after open-label treatment with HC-ER in the conversion/titration phase of the study, 74% were very much or completely satisfied with their pain medications. Over the course of the 12-week blinded maintenance phase, the proportion of the subjects very much or completely satisfied with their pain medications in

the group randomized to receive HC-ER remained high at 54%, with a lower proportion similarly satisfied in the placebo group at 35%.

Table 17: Change from Screening in Patient Global Assessment of Medication, ITT Population, Study 801

	HC-ER (N=151)		Placebo (N=151)
N	143		147
Mean (SD)	0.8 (1.27)		0.0 (1.37)
p-value		*<0.001*	

Figure 15: Proportion of Subjects Very Much or Completely Satisfied with Their Pain Medication − ITT Population, Study 801



5.2.4.3 Other Secondary Endpoints

Pivotal Study 801 was not powered to achieve significance in the other secondary efficacy endpoints. However, the secondary endpoints in this case showed a robust and consistent effect, as nearly all were statistically significant in favor of HC-ER. As anticipated in the statistical analysis plan, adjustments were not made for multiple comparisons.

5.2.4.3.1 Time to Treatment Discontinuation – Study 801

The IMMPACT group considers disposition of subjects in a clinical trial as one of the core domains for assessing chronic pain treatment efficacy and effectiveness (Turk 2003). In the maintenance treatment phase of Study 801, only 14 subjects (9%) discontinued due to lack of efficacy in the HC-ER group, compared with 64 subjects (42%) in the placebo group. Subjects in the HC-ER group had a significantly lower probability of discontinuing from treatment for lack of efficacy than those in the placebo group ($p<0.001$). A difference is readily apparent within the first 7 days of the randomized maintenance treatment phase as shown in a Kaplan-Meier plot (Figure 16), the difference in discontinuation rate continued to increase until about 30 days. The substantial difference between HC-ER and Placebo remained to the end of the study.

Subjects randomized to placebo in Study 801 were also more likely to exit the study due to adverse events (Figure 17) and for all causes (Figure 18). This suggests that the efficacy of HC-ER was not overwhelmed by its side effects.

Figure 16: Kaplan-Meier Plot of Time-to-Exit Due to Lack of Efficacy, Maintenance Treatment Phase, ITT Population, Study 801

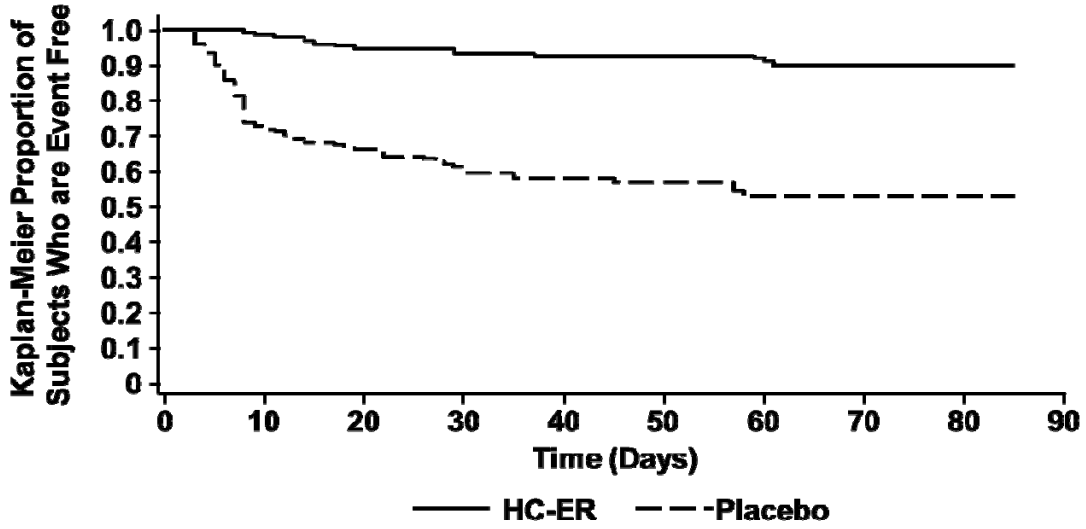


Figure 17: Kaplan-Meier Plot of Time-to-Exit Due to Adverse Event, Maintenance Treatment Phase, Study 801

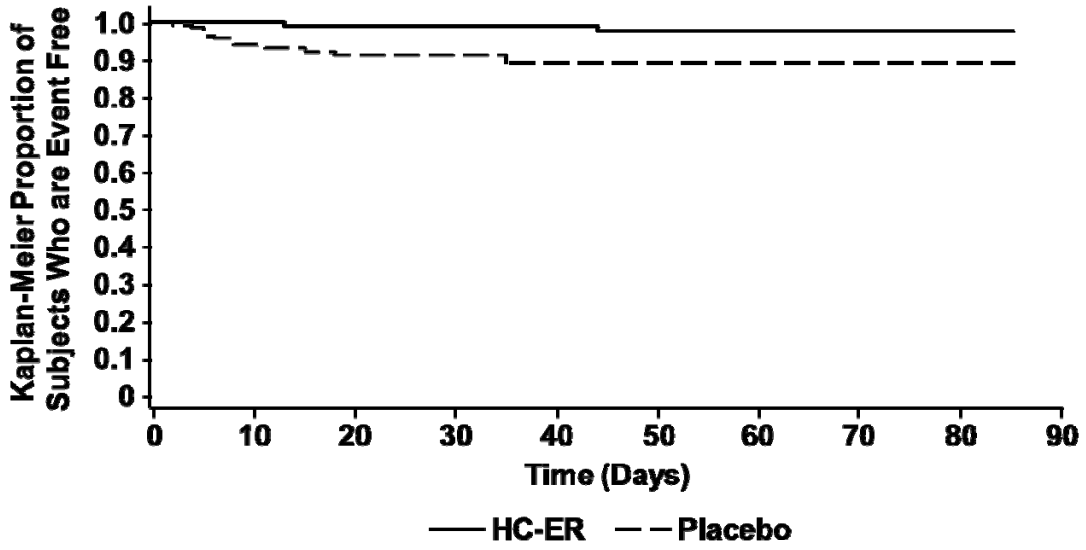
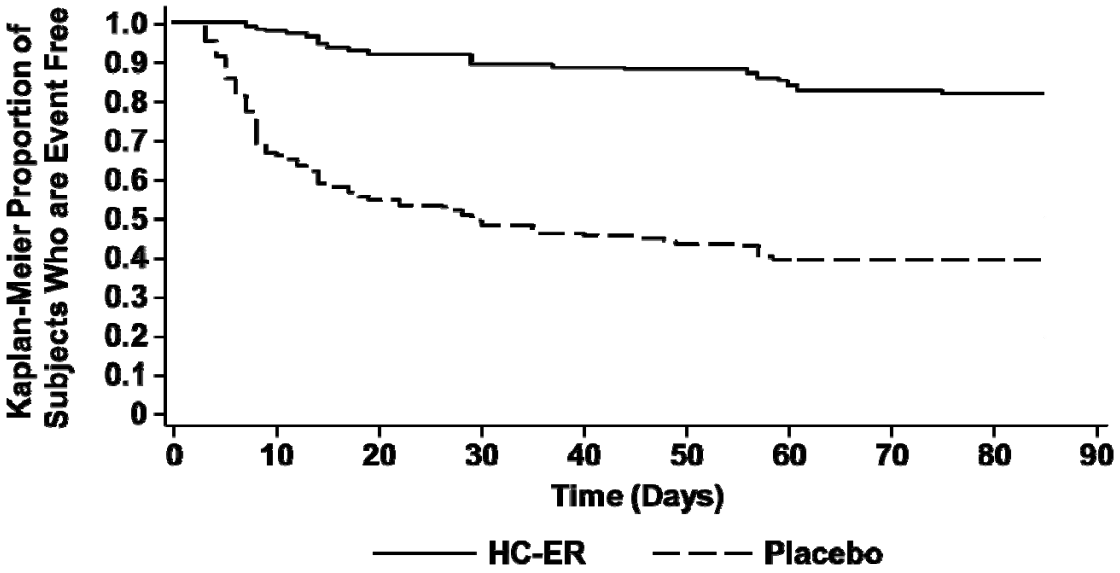


Figure 18: Kaplan-Meier Plot of Time-to-Exit Due to All Causes, Maintenance Treatment Phase, Study 801



5.2.4.3.2 Oswestry Disability – Study 801

Subjects were given a series of questions in 10 categories to answer during clinic visits at Screening, Baseline, and Day 85 (Appendix 1). The sum of individual scores was summed and divided by the highest possible score to produce the ODI, expressed as a value from 0 to 100. Results were evaluated with a treatment comparison using ANCOVA with treatment group as a fixed effect and Screening ODI score and Baseline ODI score as covariates. Disability was categorized as minimal (0-20), moderate (>20-40), severe (>40-60), crippled (>60-80), or bedridden (>80-100).

As shown in Table 18, at Day 85/last visit, mean ODI scores were reduced from Screening to the end of study, and were significantly lower for the HC-ER group (53.2 ± 13.9) compared to the placebo group (57.6 ± 16.6, p=0.026). Four points has been suggested as the minimum difference in mean scores between groups to carry clinical significance (Meade 1995).

Table 18: Change from Screening in Oswestry Disability Index, ITT Population, Study 801

	HC-ER (N=151)		Placebo (N=151)
Screening			
n	150		151
Mean (SD)	62.1 (13.7)		62.3 (12.6)
Baseline			
n	149		148
Mean (SD)	48.9 (13.5)		51 (13.3)
Day 85/Last Visit			
n	144		147
Mean (SD)	53.2 (13.9)		57.6 (16.6)
p-value[a]		*0.026*	

5.2.4.3.3 Hospital Anxiety and Depression Scale

The HADS is a validated scale that includes both an anxiety and a depression score (Zigmond and Snaith 1983). They are typically measured in clinical studies of opioid analgesics to ensure that there is no deterioration of mood while on therapy, and to potentially detect any benefit, with lower values indicative of less anxiety or depression.

There were no significant differences between treatment groups for anxiety, but subjects in the HC-ER group experienced a significant improvement in their depression compared to those in the placebo group. Mean screening anxiety scores were 5.7 ± 3.3 for the HC-ER group and 5.6 ± 3.0 for the placebo group. The change from screening to Day 85 in anxiety scores was -0.2 ± 3.6 for the HC-ER group and 0.0 ± 3.5 for the placebo group (p=0.852). Mean screening depression scores were 4.7 ± 3.4 for the HC-ER group and 4.9 ± 3.4 for the placebo group, and baseline depression scores were 3.7 ± 3.0 for the HC-ER group and 4.0 ± 3.3 for the placebo group. At Day 85, mean depression scores were 4.3 ± 3.4 for the HC-ER group and 5.6 ± 4.2 for the placebo group. The change from screening to Day 85 in depression scores was -0.4 ± 3.5 for the HC-ER group and 0.6 ± 3.7 for the placebo group. There was a significant difference between the treatment groups in change of depression score from screening to Day 85 (p=0.006). Much of the improvement in depression was observed early, between the screening and baseline visits. This suggests that once an individual is appropriately stabilized on their HC-ER dose, the benefit with respect to depression is maintained throughout treatment.

5.2.4.3.4 Rescue Medication Use

The use of rescue medication (5 mg hydrocodone/500 mg APAP) was restricted by the protocol to no more than 2 tablets per day during the treatment phase. The rescue medication results were split by two time periods: Days 1 to 14 representing the period during which blinded tapering was occurring and Days 15 to 85 once the taper was complete. The mean percentage of days that a subject took rescue medication from Days 1 to 14 was 70.5% ± 30.6% in the HC-ER group and 72.3% ± 29.1% in the placebo group. The mean number of daily rescue doses for Days 1 to 14 was 1.0 ± 0.6 in the HC-ER group and 1.1 ± 0.6 for the placebo group. The mean percentage of days that a subject took a rescue medication during Days 15 to 85 was 66.7% ± 33.1% in the HC-ER group and

71.8% ± 31.1% in the placebo group. The mean number of daily doses for Days 15-85 was 0.9 ± 0.6 and 1.1 ± 0.6 in the HC-ER group and placebo group respectively. Overall, the mean TDD of rescue medication was 6.0 mg ± 3.4 mg of HC for HC-ER subjects and 7.5 mg ± 3.9 mg HC for placebo subjects in the treatment period. These trends to increased rescue medication use in the group receiving placebo did not reach statistical significance.

5.2.4.3.5 Worst Pain Intensity

The mean change in daily worst pain intensity score from baseline to Day 85 was 0.42 ± 1.76 in the HC-ER group, and was 1.03 ± 1.79 in the placebo group. Comparing treatment groups with ANCOVA in a similar manner to the primary endpoint, the increase in daily worst pain intensity score from baseline to Day 85 was significantly lower in the HC-ER group than the placebo group (p=0.002). This indicates that HC-ER had a greater effect on worst pain intensity than did placebo. At each of the post-baseline visits (Days 8, 15, 29 and 57), the mean change in daily worst pain intensity score from baseline was lower in the HC-ER group than in the placebo group.

5.2.4.3.6 Least Pain Intensity

The mean change in daily least pain intensity score from baseline to Day 85 was 0.50 ± 1.43 in the HC-ER group, and was 0.98 ± 1.47 in the placebo group. Comparing treatment groups with ANCOVA in a manner similar to the primary endpoint, the increase in daily least pain intensity score from baseline to Day 85 was significantly lower in the HC-ER group than the placebo group (p=0.004). This indicates that HC-ER had a greater effect on least pain intensity than did placebo. At each of the post-baseline visits (Days 8, 15, 29 and 57), the mean change in daily least pain intensity score from baseline was lower in the HC-ER group than in the placebo group.

5.2.4.3.7 24-Hour Average Pain Intensity (In Clinic)

The primary endpoint analysis of Study 801 was based on 24-hour average pain intensity values recorded in the subjects' electronic diaries. Twenty-four-hour average pain intensity scores were also collected in person at each clinic visit. The change from baseline to Day 85 for the in-clinic pain scores was 0.83 ± 1.84 in the HC-ER group, and was 1.68 ± 2.12 in the placebo group. Comparing treatment groups with ANCOVA in a manner similar to the primary endpoint, the increase in 24-hour average pain intensity score from baseline to Day 85 was significantly lower in the HC-ER group than the placebo group ($p<0.001$). This confirms that HC-ER had a greater effect on 24 hour average pain intensity than did placebo. At each of the post-baseline visits (Days 8, 15, 29, and 57), the mean change in 24-hour average pain intensity score from baseline was lower in the HC-ER group than in the placebo group.

In summary, there was a consistent result of a significant result in favor of HC-ER over placebo for virtually all of these pre-specified secondary endpoints, which provide supportive data showing that compared to subjects receiving placebo, subjects treated with HC-ER experienced reduced pain, and were more likely to continue their study medication treatments.

5.2.4.4 Subgroup Efficacy Results – Study 801

In Study 801, subgroup analyses (gender, age, and race) were performed for the primary endpoint (the change from Baseline to Day 85 in average daily pain intensity score) and the two key secondary endpoints (proportion of 30% responders, change from screening in

SGAM). The results of the gender, age, and race subgroup analyses were similar to those of the overall population and generally confirmed that HC-ER was more effective than placebo in providing pain relief and satisfaction with pain medication in the subpopulations. The study population was predominantly White (80%) and 90% of subjects were in the 18 to <65 years age subgroup, therefore, statistical significance was not always achieved due to the small number of subjects in the some of the subgroups.

5.2.4.5 Efficacy Conclusions – Study 801

The efficacy of HC-ER compared to placebo was robust across a variety of standard methods for examining pain intensity in clinical trials. HC-ER was superior to placebo in relieving pain on group mean difference in pain intensity (average daily pain intensity scores, the primary study endpoint, $p=0.008$), and on measures of clinically meaningful individual improvement in pain intensity (30% response rate ($p<0.001$) and 50% response rate ($p<0.001$), which are considered "clinically important" and "major" improvement, respectively). In addition, subjects on HC-ER had a significantly longer time-to-exit due to loss of efficacy compared to placebo ($p<0.001$), which is an important and statistically powerful measure of analgesic efficacy. There was also evidence of efficacy in each of the additional domains that can demonstrate chronic pain treatment efficacy and effectiveness, when comparing HC-ER to placebo: physical functioning (lower disability scores, $p=0.026$), emotional functioning (lower depression scores, $p=0.006$), and participant ratings of global improvement (greater satisfaction with study medication, $p<0.001$).

5.2.5 Safety Results – Study 801

AE information was collected at every study visit. There was a follow-up call two weeks after the last study visit (end of study or early termination) to collect information on AEs that were ongoing at the end of the study and any new serious adverse events (SAEs) that occurred during this time period. At the time of the follow-up call, subjects had often transitioned to another chronic pain regimen that may have included another opioid. Multiple attempts were made to find subjects lost to follow-up.

5.2.5.1 Exposure – Study 801

During the conversion/titration phase, the mean exposure to HC-ER was 28 days with a mean TDD of 79 mg. The mean rescue medication dose was 10.3 mg per day hydrocodone as HC/APAP. At the end of the conversion and titration phase, subjects who were randomized to receive HC-ER had been titrated to a mean dose of 121 mg HC-ER TDD. During the 12 week maintenance treatment phase, mean exposure to HC-ER in the group randomized to receive HC-ER was 77 days with a mean TDD of 119 mg, with HC-ER doses that ranged from 40 to 200 mg per day. Subjects randomized to placebo had a taper of HC-ER during the first 2-10 days of the maintenance phase. The mean rescue medication dose was 6.0 mg hydrocodone per day in the HC-ER group, and 7.5 mg hydrocodone per day in the placebo group, both as HC/APAP.

5.2.5.2 Treatment Emergent Adverse Events – Study 801

Treatment Emergent Adverse Events (TEAEs) were experienced by 52.9% of the subjects in the conversion/titration phase of the study, by 60.3% of the subjects randomized to HC-ER in the maintenance treatment phase of the study, and by 44.4% of the subjects randomized to

Placebo in the maintenance treatment phase of the study (Table 19). The majority of TEAEs were mild or moderate in severity. Despite the overall rate of TEAE frequency being higher in the HC-ER group than the placebo group, a smaller proportion of subjects in the HC-ER group (2%) relative to the placebo group (11%) experienced an AE that led to study discontinuation.

Zogenix adopted a strict policy of capturing any suspected episode of study drug diversion as an administrative SAE; these events are discussed in greater detail in Section 5.2.1 of this briefing document.

Table 19: Summary of TEAEs, Safety Population, Study 801

	Conversion/ Titration	Maintenance Treatment	
	HC-ER (N=510)	HC-ER (N=151)	Placebo (N=151)
Subjects with at least one TEAE	270 (52.9%)	91 (60.3%)	67 (44.4%)
Deaths	0	0	0
Subjects with medical TEAE leading to discontinuation	39 (7.6%)	2 (1.3%)	9 (6.0%)
Subjects with at least one medical SAE	6 (1.2%)	5 (3.3%)	0

5.2.5.3 AEs Leading to Discontinuation – Study 801

In the open-label conversion/titration phase of the study, 39 subjects (8%) discontinued the study due to a medical adverse event (Table 19). The most frequent AEs were nausea (3%), constipation (1%), and vomiting (1%).

In the double-blind maintenance treatment phase, 2 subjects (1%) in the HC-ER group discontinued the study due to a medical adverse event (Table 19); 1 each for back pain and diarrhea. Nine subjects in the Placebo group discontinued the study due to a medical AE, with 4 (3%) discontinued due to withdrawal syndrome, and all other events (depression, insomnia, fatigue, pain, muscle spasms, ear infection, decreased appetite, hyperhidrosis and hot flush) were each reported by 1 subject each.

5.2.5.4 Serious Adverse Events – Study 801

There were no deaths in the study.

During the conversion/titration phase, 6 subjects (1%) reported at least one SAE. The serious episodes were: anxiety; non-cardiac chest pain; chronic obstructive pulmonary disease; joint instability; hematemesis; and angina pectoris.

During the double-blind maintenance treatment phase, 5 subjects (3%) in the group randomized to receive HC-ER reported SAEs. The events were: depression and homicidal ideation; abdominal distention, diarrhoea, nausea, and hypokalemia; intervertebral disc disorder; ovarian abscess; and non-cardiac chest pain, and anemia. There were no SAEs in the group randomized to receive placebo.

5.2.5.5 Common Adverse Events – Study 801

TEAEs that occurred at incidence rates of ≥2% in either treatment group in the double-blind treatment period are provided in Table 20. Overall the most commonly occurring TEAEs in the HC-ER group were: constipation (7.9%), nausea (7.3%), urinary tract infection (5.3%), vomiting (4.6%) and back pain (4.0%). The most commonly occurring TEAEs in the placebo group were: withdrawal syndrome (6.0%), diarrhea (5.3%) and insomnia (4.6%). Hypoacusis (decreased hearing sensation) was reported in both the HC-ER group (3.3%) and the Placebo group (2.6%) and is discussed in Section 5.2.5.7 of this briefing document.

Table 20: TEAEs Experienced by ≥2% of Subjects During the Double-blind Treatment Phase by Preferred Term, Safety Population, Study 801

Preferred Term	HC-ER (N=151)	Placebo (N=151)
Nausea	11 (7.3%)	5 (3.3%)
Constipation	12 (7.9%)	0 (0.0%)
Diarrhea	4 (2.6%)	8 (5.3%)
Back pain	6 (4.0%)	5 (3.3%)
Urinary tract infection	8 (5.3%)	3 (2.0%)
Insomnia	3 (2.0%)	7 (4.6%)
Withdrawal syndrome	1 (0.7%)	9 (6.0%)
Hypoacusis	5 (3.3%)	4 (2.6%)
Vomiting	1 (0.7%)	8 (2.6%)
Sinusitis	4 (2.6%)	7 (2.3%)

5.2.5.6 Adverse Events by Subpopulation – Study 801

As is common in opioid studies, women reported more TEAEs than men; however, the frequency and types of events were similar in both genders. The numbers of subjects in the racial subgroups and in the elderly were too small to support any conclusions regarding relationship of TEAEs and race or age group.

5.2.5.7 Audiometry – Study 801

Audiometry testing was incorporated into Study 801 by request of the Agency because of reports of hearing loss associated with the abuse of HC/APAP (Media Awareness Project; Ishiyama 2001; Ho 2007). Audiometry was performed for each subject at screening, baseline and Day 85, and a comparison of changes over time of individual audiometry results was undertaken according to predefined criteria. The pure tone audiology results were also reviewed by a central reader, a clinical audiologist.

Overall, 1257 audiometric panels were conducted in 510 subjects throughout the study; none were found to demonstrate clinically significant progressive hearing loss or hearing loss related to study medication, and no subjects had a self-report of hearing loss (discernible hearing problem or hearing deficit) during their participation in the study or at the 2-week post-study follow-up. Due to strict criteria established for the audiometry testing and the requirement to report certain test results as AEs regardless of clinical findings, hypoacusis was reported as a TEAE at low but similar rates in the HC-ER group (3.3%) and the Placebo group (2.6%; Table 20).

5.2.5.8 Clinical Laboratory Test Results, Vital Signs, Physical Examinations – Study 801

No clinically important differences between the HC-ER and Placebo groups were noted for clinical laboratory results, vital signs, or physical exams during the study.

5.2.5.9 Clinical Opioid Withdrawal Scale and Subjective Opioid Withdrawal Scale – Study 801

The Clinical Opioid Withdrawal Scale (COWS) and Subjective Opioid Withdrawal Scale (SOWS) were used in this study as tools to aid the clinicians in the assessment of opioid withdrawal. Higher COWS and SOWS scores indicate more severe withdrawal symptoms.

No clinically important differences between the HC-ER and placebo groups with the SOWS were observed during the study. Placebo subjects were slightly worse over the course of the double-blind maintenance treatment phase compared to HC-ER treated subjects on the COWS. All subjects in the HC-ER group were categorized in the 'no withdrawal' category throughout the double-blind maintenance treatment phase for both COWS and SOWS. Subjects in the placebo group also maintained a 'no withdrawal' category when evaluated with the SOWS; however, when utilizing the COWS alone the majority of placebo subjects (79%) remained in the 'no withdrawal' group, 19% of subjects were rated in the 'mild withdrawal' category, and 2% of subjects were rated in the 'moderate withdrawal' category. According to the study design, subjects were allowed rescue medication (5 mg hydrocodone/500 mg APAP) during the course of the double-blind maintenance treatment phase, which may have contributed to the low number of withdrawal instances.

5.2.5.10 Safety Conclusions – Study 801

HC-ER was generally safe and well-tolerated in Study 801. No subject died during the course of the study. Serious medical adverse events associated with HC-ER were few in number, and mainly represented concurrent medical events that were not plausibly related to HC-ER use. Commonly reported AEs by preferred term included constipation, nausea and somnolence.

The overall pattern and nature of AEs experienced by subjects taking HC-ER was consistent with the expected AEs common with other opioid medications (see also Section 5.4.2). No new or unexpected safety concerns were observed with the use of HC-ER in this study. The twice daily regimen of HC-ER at doses of 40-200 mg per day appeared to be well-tolerated, with no treatment-related AE leading to study discontinuation once a stabilized dose had been attained.

5.2.6 Compliance – Study 801

Zogenix employed a variety of techniques in the HC-ER clinical development program to prospectively prevent abuse and diversion, including 1) patients were excluded with past or present alcohol or drug abuse or serious psychiatric disorders; 2) all drug accountability issues without plausible medical justification were considered possible diversions and recorded as SAEs; and 3) events of significant loss or diversion were reported to the local authorities and the DEA.

HC-ER and placebo were distributed in numbered blister packs and rescue medicine was distributed as numbered bottles of HC/APAP. Subjects were required to record every dose of study medication and rescue medication in an electronic diary which applied a date/time stamp. At every visit, all medication packages (empty, full or part-full) and the diary were reviewed. Returned study medication was counted and witnessed in front of the subject and logged with all three signatures. The study staff compared the medication counts to the diary entries and discussed them with the subject.

A compliance index was calculated by dividing the number of doses of study medication taken by the number of doses that were predicted based on the assigned dosing regimen, and expressed as a percentage. The proportion of subjects who had a compliance index above 90% in the maintenance treatment phase of Study 801 was 96% in the HC-ER group and 93% in the placebo group.

5.2.6.1 Drug Accountability – Study 801

Drug accountability data were analyzed to calculate the amount of missing drug, expressed as the amount of missing drug (units that should have been returned but were not) divided by the total number of units of drug that were dispensed during the study. Case report form data suggested that < 2% of the total number of dispensed HC-ER capsules could be considered missing and < 3% of the dispensed rescue HC/APAP tablets could be considered missing. These outcomes appear to compare favorably to a 36% value for missing drug from a FDA Controlled Substance Staff (CSS) analysis of pivotal study data at the September 23, 2009 joint meeting of the Anesthetic Life Support Drugs Advisory Committee with the Drug Safety and Risk Management Advisory Committee to consider the Exalgo NDA.

5.2.6.2 Investigation of Suspected Diversion - Study 801

A total of 24 subjects had drug accountability issues identified during Study 801 that were investigated as potential diversion. Seventeen were in the conversion/titration phase of the study, and seven were in the maintenance treatment phase of the study (4 subjects randomized to placebo and 3 subjects randomized to HC-ER). In 7 of the 24 instances, the investigator and sponsor agreed that the accountability issue was plausibly an error or accident, and the subject was allowed to continue on study; the remaining 17 subjects were discontinued from the study for noncompliance. The amount of study medication involved in the 24 drug accountability cases totaled 301 capsules of HC-ER and 534 tablets of HC/APAP. This represented 0.19% of the HC-ER dispensed over the course of the study, and 0.53% of the HC/APAP dispensed over the course of the study.

In addition, verbatim adverse event terms were searched for any evidence of abuse, misuse or overdose. One subject in Study 801 had a TEAE term of abuse, and four had a TEAE term of misuse. One subject had a verbatim term of overdose that was consuming more than the prescribed amount of study medication.

One study site was closed for cause during the course of Study 801. Early in the study, multiple Good Clinical Practice violations were documented by the study monitor and confirmed by an independent audit. Both the sponsor's assessment and the independent audit found repeated instances of noncompliance with regard to study conduct, subject selection and subject safety, investigator oversight, custodial responsibility of study drug, and appropriate and timely communication with the sponsor's staff and medical monitor. Five subjects had been enrolled in the study; four had already gone off study during the conversion/titration phase, and one who was randomized to placebo was discontinued by the sponsor. Appropriate federal, state, and local agencies, including the FDA Office of Compliance (Division of Scientific Investigation), the DEA, the Institutional Review Board, and the state medical board were informed of the 'for cause' site closure. All study medication, including blinded study drug and rescue medication, was accounted for at the time of closure.

5.2.6.3 Compliance Conclusion - Study 801

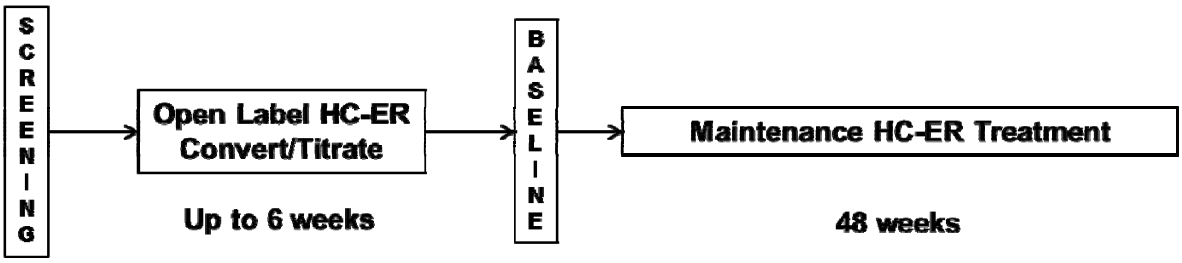
Zogenix recognizes that their new formulation of ER hydrocodone has the potential for significant abuse, probably not less than other current approved opioids. The rigorous and vigilant oversight and compliance program that was undertaken and executed during the registration clinical program was representative of the company's attitudes and planned philosophy for marketing Zohydro ER. Zogenix believes that there is a strong medical need for this product, but that it must be introduced into clinical usage with appropriate safeguards and oversight. The company's experiences and policies during the clinical trials represent an excellent framework of responsible prescribing, vigorous training and education, and vigilant oversight with immediate and aggressive corrective actions that foreshadows the Zogenix approach to commercializing Zohydro ER in the most responsible manner possible.

5.3 Safety Study 802

5.3.1 Study Design – Study 802

Study 802 was a multicenter, long-term, open-label, safety study that used an EERW. Study 802 consisted of three distinct periods (Figure 19).

Figure 19: Study Design – Study 802



- Screening to determine eligibility to enter the study.
- Open-label conversion and titration phase (up to 6 weeks), where subjects were converted from their previous opioid therapy to HC-ER, and then had their HC-ER dose titrated based on pain relief and tolerance to obtain an individual stabilized dose.
- Eligibility determination for maintenance treatment (Baseline).
- Open-label maintenance treatment phase, 48 weeks in duration.

5.3.1.1 Screening, Inclusion/Exclusion

At Screening, subjects were eligible to enter the study if they were diagnosed with a chronic, moderate-to-severe pain condition treated with, or eligible for treatment with, around-the-clock opioid therapy for at least three months prior to study entry, and had been taking opioids for at least 5 days/week for the past 4 weeks at the equivalent of at least an average daily dose of 30 mg hydrocodone (i.e., 45 mg oral morphine equivalents per day). Subjects at screening also were required to have stable adjunctive regimens (e.g., physical therapy, biofeedback therapy); were in generally good health; were able to effectively communicate with the study staff and able to complete study procedures; and voluntarily provided written informed consent.

Subjects were excluded from entering the study if they: had any condition that would increase the risk of opioid-related adverse events (e.g., chronic carbon dioxide retention, respiratory depression, chronic constipation, gastroparesis, inflammatory bowel disease, active seizure disorder); had a history of any illicit substance or alcohol abuse in the past 5 years or any history of opioid abuse; had a positive urine drug screen for illicit drugs, or non-prescribed controlled substances; had a HADS index score of >12 in either depression or anxiety subscales or an established history of major depressive disorder that was poorly controlled with medication, had a surgical procedure for pain within 3 months; had uncontrolled hypertension; had a BMI >45 kg/m^2; had a clinically significant abnormality in clinical chemistry, hematology or urinalysis; had active or pending workman's compensation or litigation case related to their pain; had a known allergy or hypersensitivity to opioids; had

a history of clinically significant intolerance to hydrocodone; had a history of intolerance to acetaminophen; had taken any investigational drug within 30 days prior to the Screening visit or was currently enrolled in another investigational drug study; or had used a monoamine oxidase inhibitor within 14 days.

5.3.1.2 Open-Label Conversion/Titration Phase

During the open-label conversion/titration phase, subjects were initially converted to a dosage of HC-ER that was approximately 20%-30% less than the equianalgesic dose of HC-ER calculated based on their prior opioid treatment. After conversion, if the subject did not achieve satisfactory analgesia with the initial dose, the subject was titrated, in an open-label fashion to their individual optimum HC-ER dose. Rescue medication (hydrocodone 5 mg/acetaminophen 500 mg) was supplied by Zogenix, and up to 4 tablets per day were permitted as supplemental pain medication due to inadequate pain relief. A stabilized dose was one that subjects tolerated well for at least 7 days with an average 24 hour daily average pain score of ≤4 on the NRS during the last 7 days prior to Baseline, and subjects were taking no more than 2 tablets of rescue medication on any day. Subjects who did not achieve a stabilized dose, who did not tolerate HC-ER treatment due to adverse events, who were not compliant with dosing or drug accountability, or who could not complete required study procedures (e.g. study visits, use of subject diary) were discontinued from the study.

5.3.1.3 Maintenance Treatment Phase

Subjects were eligible for long-term maintenance treatment phase if they: had been stabilized on at least 40 mg HC-ER per day; had reached a stabilized dose within 6 weeks of open-label treatment; had tolerable side effects and were willing to stay on the medication for the duration of the study; had been compliant with diary completion and drug accountability procedures; and had an average 24-hour daily average pain score of ≤4 on the NRS during the last 7 days prior entering the long-term maintenance treatment phase.

During the 48-week maintenance treatment phase of the study, subjects were continued on their stabilized dose of at least 40 mg HC-ER per day, taken every 12 hours. The HC-ER dose could be adjusted up or down in predetermined increments at the discretion of the Investigator at any time for reasons of efficacy or tolerability. Up to 2 tablets of sponsor-provided HC/APAP (5 mg/500 mg) were permitted each day as rescue medication. Subjects who were not compliant with study medication administration or accountability, or who could not complete required study procedures were discontinued from the study.

All other opioid medications, monoamine oxidase inhibitors, and any other investigational drug were prohibited throughout the study. Non-opioid pain medication, aspirin, CNS depressants, muscle relaxants, sedative, antidepressants, anticonvulsants, benzodiazepines, inhaled steroids, physical therapy, biofeedback therapy, acupuncture therapy, and herbal remedies could not be started during the conversion/titration phase, but a stable pre-study regimen could be continued. Free use of non-exclusionary concomitant drug(s) and therapies was permitted during the treatment phase. However, for worsening pain, the Investigator first titrated study medication prior to initiating any other non-opioid analgesic therapy (i.e.,

starting a new non-opioid analgesic or other new pain medication, or increasing the dose of a current concomitant non-opioid analgesic or other pain medication or therapy).

5.3.1.4 Sample Size

It was estimated that 600 subjects needed to be enrolled to achieve a sufficient sample size to evaluate at least 100 subjects exposed to HC-ER for 1 year and 300 subjects exposed for at least 6 months.

5.3.2 Demographics – Study 802

The study was conducted at 56 sites across all regions of the continental US between June 2010 and December 2011. The demographic characteristics of the 638 subjects who were enrolled in the study and were treated with HC-ER in the conversion/titration phase of the study are shown in Table 21. The mean age of subjects was 51 years; the majority were female (56%) and White (81%). The screening average pain score was 6.4. Subjects entered the study with chronic pain conditions of various etiologies, and many subjects had multiple pain types including arthritis (45%), low back pain (40%), and neuropathic pain (30%).

For the set of subjects entering the maintenance phase of the study, the disability score (ODI) was 41.2 out of 100. The Baseline average pain score was 3.1, which decreased from 6.4 at study entry after open-label treatment with HC-ER.

Table 21: Demographic characteristics at Study Entry, Study 802

	Conversion/ Titration Phase (N=638)	Maintenance Treatment Phase (N=424)
Age (years)		
Mean (SD)	50.9 (10.93)	50.7 (10.99)
Range	20-75	20-75
Sex		
Male	278 (43.6%)	185 (43.6%)
Female	360 (56.4%)	239 (56.4%)
Race		
White	518 (81.2%)	337 (79.5%)
Black or African American	107 (16.8%)	77 (18.2%)
Other	13 (2.0%)	10 (2.4%)
BMI (kg/m2)		
Mean (SD)	30.1 (6.35)	30.1 (6.41)
Range	17-49	17-49
Average Pain Score at Screening (Before Titration)		
Mean (SD)	6.4 (1.72)	6.4 (1.77)
Median	6.0	6.0
Range	1-10	1-10
Prestudy Opioid Usage (mg/day MS equivalents)		
Mean (SD)	103.3 (93.35)	94.7 (76.92)
Range	30-720	30-645
Oswestry Disability Index		
Mean (SD)	-	41.2 (14.87)
Range	-	30-78
Average Pain Score at Baseline (After Titration)		
Mean (SD)	-	3.1 (1.09)
Range	-	0-7

5.3.3 Subject Disposition – Study 802

638 subjects with chronic pain were enrolled in Study 802. A total of 424 subjects (66%) entered the maintenance treatment phase, and 214 (34%) discontinued during the conversion/titration phase of the study. A total of 285 (67%) of the 424 subjects who entered the maintenance phase completed the study (Table 22). The most common reason for discontinuation from the conversion/titration phase (68 subjects, 10.7%) was 'Protocol specified criteria', which included failure to reach a stabilized dose of HC-ER within 6 weeks of open-label treatment, failure to reach an absolute score of ≤4 on the NRS pain scale, positive drug screen, or use of prohibited concomitant medication (Table 22). The next most common reason for discontinuation from the conversion/titration phase was noncompliance (53 subjects, 8.3%), which included failure to report daily pain scores and study drug accountability information, excessive use of rescue medication, and drug accountability issues. AEs during the conversion/titration phase led to discontinuation for 56 subjects (8.8%), and are discussed in Section 5.3.4.5. These discontinuation rates do not appear to be different from those observed in enriched enrollment studies of other ER opioids (Section 5.2.3.3).

Of the 424 subjects who entered the maintenance treatment phase, a total of 285 subjects (67%) completed the study. There were 139 subjects (33%) who discontinued before the end of the 48-week maintenance treatment period. The most common reason for early discontinuation was noncompliance (11%), followed by AE (9%), and withdrawal of consent (6%). Given that the maintenance treatment phase lasted for close to one year, the incidence of withdrawals (55.3% over a 1-year period) is within expectations. For example, 54%-65% of subjects discontinued during a one year study of tapentadol vs. oxycodone (Wild 2010).

Table 22: Reasons for early discontinuation, Study 802

Reasons for discontinuation	Conversion/Titration Phase (N=638)	Maintenance Treatment Phase (N=424)
Number of Subjects	214 (33.5%)	139 (32.8%)
Protocol specified criteria	68 (10.7%)	9 (2.1%)
Noncompliance	53 (8.3%)	48 (11.3%)
Adverse event	56 (8.8%)	40 (9.4%)
Withdrew consent	26 (4.1%)	27 (6.4%)
Withdrawn by Investigator	5 (0.8%)	3 (0.7%)
Opioid withdrawal	3 (0.5%)	2 (0.5%)
Lost to follow-up	3 (0.5%)	8 (1.9%)
Other	0	2 (0.5%)

5.3.4 Safety Results – Study 802

AE information was collected at every study visit. There was a follow-up call two weeks after the last study visit (end of study or early termination) to collect information on AEs that were ongoing at the end of the study and any new SAEs that occurred during this time period. At the time of the follow-up call, subjects had generally transitioned to another chronic pain regimen that may have included a different opioid. Multiple attempts were made to find subjects lost to follow-up.

5.3.4.1 Exposure – Study 802

During the conversion and titration phase, the mean exposure to HC-ER was 30 days with a mean TDD of 99 mg HC-ER (Table 23).The mean rescue medication dose in the conversion and titration phase was 11.2 mg per day hydrocodone as HC/APAP.

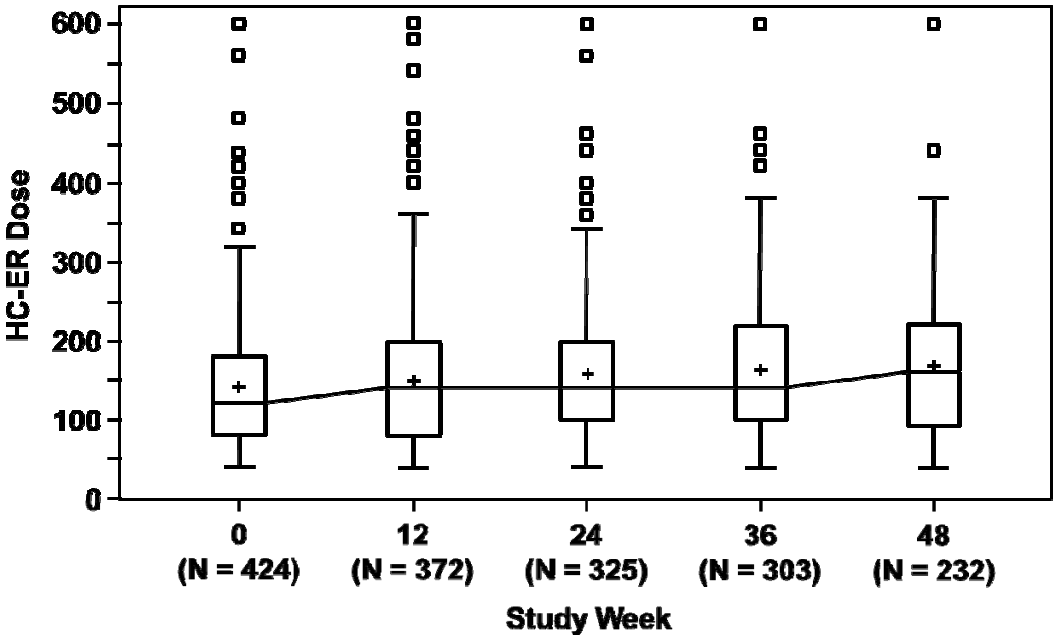
During the 48-week maintenance treatment phase, mean exposure to HC-ER was 267 days with a mean TDD of 149 mg HC-ER. A box and whisker plot of HC-ER TDD over time for the maintenance treatment phase is shown in Figure 20. The dose of HC-ER used by study subjects was relatively stable over the course of the 48-week study, with a mean and median daily dose of HC-ER that were both approximately 150 mg HC-ER, and which rose only modestly over time. Few subjects required more than 350 mg HC-ER per day. There were 109 patients (38%) who completed the study with no increase in dosage, and 29 subjects (10%) who completed the study with greater than a 100% change (increase) in dose. The mean rescue medication dose in the maintenance treatment phase was 6.7 mg per day hydrocodone as HC/APAP.

To place these values in context, maximum doses of other recently approved ER opioids that were tested in similar studies ranged from 400 mg to over 2,500 mg of hydrocodone equivalents per day, based on the peer-reviewed publications of their clinical trials (Katz 2010; Schwartz 2011; Portenoy 2007; Hale 2007).

Table 23: Exposure – Study 802

Exposure	Conversion/Titration Phase (N=638)	Maintenance Treatment Phase (N=424)
Total Daily Dose (mg)		
Mean (SD)	98.9 (65.72)	149.3 (88.76)
Range	0-519	0-616
Duration of Exposure (days)		
Mean (SD)	29.7 (12.76)	266.5 (112.98)
Range	1-57	1-359

Figure 20: HC-ER Dose Over Time, Maintenance Treatment Period, Safety Population, Study 802



Median dose values are connected, the boxes show the 25th and 75th percentiles, and the error bars are 1.5 times the interquartile range. Crosses represent the mean. Small boxes represent the outliers (>1.5 times IQR).

5.3.4.2 Treatment Emergent Adverse Events – Study 802

TEAEs were experienced by 63.3% of the subjects in the conversion/titration phase of the study, and by 83.5% of the subjects in the maintenance treatment phase of the study (Table 24). Some of the difference is due to the longer duration of the maintenance treatment phase (48 weeks vs. up to 6 weeks of conversion/titration). The majority of TEAEs were mild or moderate in severity.

Zogenix adopted a strict policy of capturing any suspected episode of study drug diversion as an administrative SAE; these administrative serious TEAEs are discussed in greater detail in Section 5.3.6 of this briefing document.

Table 24: Summary of TEAEs, Safety Population, Study 802

	Conversion/Titration Phase (N=638)	Maintenance Treatment Phase (N=424)
Subjects with at least one TEAE	404 (63.3%)	354 (83.5%)
Deaths	0	4 (0.9%)
Subjects with medical TEAE leading to discontinuation	42 (6.6%)	34 (8.0%)
Subjects with at least one medical SAE	16 (2.5%)	51 (12.0%)

5.3.4.3 Adverse Events Leading to Discontinuation – Study 802

In the open-label conversion/titration phase of the study, 42 subjects (7%) discontinued the study due to a medical adverse event (Table 25). The most frequent TEAEs leading to study discontinuation were nausea (1.6%), somnolence (1.4%), insomnia (1.1%), lethargy (1.1%) and headache (1.1%).

In the maintenance treatment phase, a total of 34 subjects (8%) were discontinued due to a medical adverse event (Table 25). No adverse event commonly led to discontinuation, but upper abdominal pain, cognitive disorder, and constipation were each reported by 2 subjects each.

Table 25: Medical TEAEs That Led to Discontinuation of ≥2 Subjects In Either Phase, Safety Population, Study 802

	Conversion/Titration Phase N=638	Maintenance Treatment Phase N=424
Subjects with at least 1 event	42 (6.6%)	34 (8.0%)
Nausea	10 (1.6%)	1 (0.2%)
Somnolence	9 (1.4%)	1 (0.2%)
Insomnia	7 (1.1%)	1 (0.2%)
Lethargy	7 (1.1%)	0
Headache	7 (1.1%)	0
Vomiting	4 (0.6%)	0
Constipation	3 (0.5%)	2 (0.5%)
Edema peripheral	3 (0.5%)	0
Dizziness	2 (0.3%)	1 (0.2%)
Irritability	2 (0.3%)	1 (0.2%)
Arthralgia	2 (0.3%)	1 (0.2%)
Pruritus allergic	2 (0.3%)	0
Drug withdrawal syndrome	2 (0.3%)	0
Feeling jittery	2 (0.3%)	0
Abdominal pain upper	0	2 (0.5%)
Cognitive disorder	0	2 (0.5%)

For those subjects who were able to achieve a stabilized dose of HC-ER and enter the maintenance treatment phase, the incidence of TEAEs that led to discontinuation was relatively low since subjects had appropriately acclimated to study drug during the conversion/titration phase.

5.3.4.4 Serious Adverse Events – Study 802

5.3.4.4.1 Deaths

No subject died during the conversion/titration phase. There were 4 subjects (0.9%) who died during the maintenance treatment phase:

- Subject 106-15, age 52 died due to suicide. The subject had a history of depression and anxiety. She had experienced worsening of anxiety starting on Drug Day 50 (relative to start of study drug), considered possibly related to treatment. The investigative site was informed that the subject committed suicide by closing herself in a garage with a car motor running. The death was considered unlikely to be related to the study drug.
- Subject 134-07, age 33 died due to mixed drug toxicity. On Drug Day 233, she complained of a moderate influenza-like illness (unrelated to treatment). Two days later she was found dead in her bed. Toxicological postmortem analyses revealed the presence of caffeine, methadone, oxycodone, diazepam, nordiazepam, oxazepam, and temazepam but only traces of hydrocodone. The cause of death was determined to be mixed drug toxicity (methadone and oxycodone). The death was considered unlikely to be related to the study drug.
- Subject 211-24, age 68 died due to lung cancer. Unresectable Stage IV non-small cell lung cancer was diagnosed on Drug Day 110. She refused cancer treatment and remained

on study and died of metastatic lung cancer on Day 262. The death was considered unlikely to be related to the study drug.
- Subject 229-10, age 59 died from atherosclerotic coronary artery disease on Drug Day 214. The event was considered not related to study drug.

5.3.4.4.2 SAEs – Study 802

A total of 16 subjects (2.5%) experienced serious medical adverse events (SAEs) in the conversion/titration phase of the study, and 51 subjects (12.0%) experienced medical SAEs in the maintenance treatment phase of the study (Table 26). One possible reason for the larger proportion of subjects reporting SAEs in the maintenance treatment phase is its longer duration (48 weeks) and greater exposure to HC-ER (Table 23). The majority of SAEs were deemed unrelated to study drug.

During the conversion/titration phase, the only medical SAE reported in more than 1 subject was non-cardiac chest pain, which was reported in 2 subjects (Table 26). Other SAEs in one subject each were: cystitis, enterococcal infection, gastroenteritis, pneumonia, sepsis, urinary tract infection, viral infection, atrial fibrillation, cardiac failure congestive, coronary artery disease, myocardial infarction, chest pain, gastric ulcer, retroperitoneal haemorrhage, OA, pain in extremity, acute respiratory failure, chronic obstructive pulmonary disease, pulmonary embolism, blood potassium decreased, lethargy, mental impairment, hypertension, and venous insufficiency.

During the maintenance treatment phase, the most frequently-reported medical SAEs (Table 26) were chronic obstructive pulmonary disease (5 subjects or 1.2%), OA (4 subjects or 0.9%), pneumonia (3 subjects or 0.7%), and small intestinal obstruction, intentional overdose, and dehydration (each reported by 2 subjects or 0.5%). Other SAEs in one subject each were: abscess limb, cellulitis, diverticulitis, extradural abscess, gastroenteritis, gastroenteritis viral, influenza, mastitis, esophageal candidiasis, pathogen resistance, pneumonia staphylococcal, pyelonephritis, sepsis, staphylococcal bacteremia, staphylococcal sepsis, urinary tract infection, viral infection, ankle fracture, drug toxicity, gunshot wound, incisional hernia, procedural pain, skull fracture, dizziness, mental impairment, myasthenia gravis, syncope, transient ischemic attack, tremor, constipation, erosive esophagitis, gastritis, ileitis, pancreatitis, back pain, intervertebral disc degeneration, joint instability, musculoskeletal chest pain, completed suicide, depression, suicidal ideation, suicide attempt, arteriosclerosis coronary artery, atrial fibrillation, non-cardiac chest pain, chest pain, asthma, pulmonary embolism, respiratory failure, hypokalemia, breast cancer, non-small cell lung cancer stage IV, anemia, lipase increased, and deep vein thrombosis.

Table 26: Serious Adverse Events in ≥ 2 Subjects In Either Phase, Safety Population, Study 802– Study 802

	Conversion/Titration Phase N=638	Maintenance Treatment Phase N=424
Subject with at least 1 event	16 (2.5%)	51 (12.0%)
COPD	1 (0.2%)	5 (1.2%)
Osteoarthritis	1 (0.2%)	4 (0.9%)
Pneumonia	1 (0.2%)	3 (0.7%)
Small intestinal obstruction	0	2 (0.5%)
Intentional overdose	0	2 (0.5%)
Dehydration	0	2 (0.5%)
Non-cardiac chest pain	2 (0.3%)	1(0.2%)

Of the 67 subjects who experienced SAEs during this study, only 2 events (mental impairment and lethargy) in 1 subject in the conversion/titration phase and 2 events (mental impairment and constipation) in 1 subject each in the maintenance treatment phase were considered possibly related to study drug.

5.3.4.5 Common Adverse Events – Study 802

TEAEs that occurred at incidence rates of ≥ 2% in either treatment phase are provided in Table 27. The most frequently-reported TEAE in the conversion/titration phase were constipation (11.3%), nausea (10.7%), somnolence (7.7%), headache (7.5%), vomiting (2.1%), insomnia (3.8%), fatigue (3.6%), and diarrhea (3.1%). The most frequently-reported TEAE in the maintenance treatment phase were constipation (12.5%), back pain (11.1%), nausea (9.9%), vomiting (9.7%), arthralgia (7.8%), headache (6.8%), and urinary tract infection (6.6%).

This pattern of AEs was expected and represents the typical opioid-associated effects on the GI and neurological systems. The occurrence of back pain and arthralgia is within clinical expectations for this population, as large percentages of subjects had low back pain or arthritis as an underlying pain condition. Opioid treatment has been associated with urinary retention, a contributing factor for urinary tract infections. There were 28 falls reported in Study 802. The study was conducted over the winter and included sites where snow and ice are common. Two falls were considered probably related to study medication, and only one resulted in a fracture (kneecap). There was no apparent relationship between the dose of HC-ER and the prevalence of fall-related TEAEs.

Overall the most common side effects were similar for the two phases of the study. GI effects were the primary adverse effects with constipation the leading adverse event reported overall. No new or unexpected adverse events were discovered in this analysis, which shows that HC-ER treatment is associated with the type and frequency of adverse events that are typical of opioids and ER opioids in particular. For example, the package insert for Exalgo indicates adverse rates of constipation (31%), nausea (28%), vomiting (14%), somnolence (15%) and

headache (12%, Exalgo Prescribing Information). For OxyContin, the AE rates (vs. placebo) are constipation (23% vs. 7%), nausea (23% vs. 11%), somnolence (23% vs. 4%), dizziness (13% vs. 9%), pruritus (13% vs. 2%) and vomiting (12% vs. 7; Oxycontin Prescribing Information).

Table 27: TEAEs Experienced By ≥ 2% of Subjects by Preferred Term, Safety Population, Study 802

Preferred Term	Conversion/Titration Phase (N=638)	Maintenance Treatment Phase (N=424)
Number of subjects with at least one event	404 (63.3%)	354 (83.5%)
Constipation	72 (11.3%)	53 (12.5%)
Back pain	9 (1.4%)	47 (11.1%)
Nausea	68 (10.7%)	42 (9.9%)
Vomiting	26 (4.1%)	41 (9.7%)
Arthralgia	9 (1.4%)	33 (7.8%)
Headache	48 (7.5%)	29 (6.8%)
Urinary tract infection	6 (0.9%)	28 (6.6%)
Fall	8 (1.3%)	25 (5.9%)
Upper respiratory tract infection	7 (1.1%)	25 (5.9%)
Nasopharyngitis	11 (1.7%)	24 (5.7%)
Anxiety	8 (1.3%)	23 (5.4%)
Sinusitis	9 (1.4%)	23 (5.4%)
Insomnia	24 (3.8%)	21 (5.0%)
Bronchitis	10 (1.6%)	20 (4.7%)
Influenza	4 (0.6%)	20 (4.7%)
Neck pain	3 (0.5%)	19 (4.5%)
Musculoskeletal pain	4 (0.6%)	18 (4.2%)
Somnolence	49 (7.7%)	18 (4.2%)
Diarrhea	20 (3.1%)	17 (4.0%)
Depression	6 (0.9%)	16 (3.8%)
Muscle spasms	11 (1.7%)	16 (3.8%)
Fatigue	23 (3.6%)	15 (3.5%)
Pyrexia	11 (1.7%)	15 (3.5%)
Contusion	4 (0.6%)	14 (3.3%)
Edema peripheral	14 (2.2%)	14 (3.3%)
Pain in extremity	7 (1.1%)	14 (3.3%)
Dizziness	18 (2.8%)	13 (3.1%)
Muscle strain	9 (1.4%)	13 (3.1%)
Migraine	5 (0.8%)	11 (2.6%)
Osteoarthritis	2 (0.3%)	11 (2.6%)
Gastroenteritis viral	6 (0.9%)	10 (2.4%)
Cough	6 (0.9%)	9 (2.1%)
Paresthesia	1 (0.2%)	9 (2.1%)
Pneumonia	3 (0.5%)	9 (2.1%)
Toothache	2 (0.3%)	9 (2.1%)
Allergic pruritus	13 (2.0%)	0

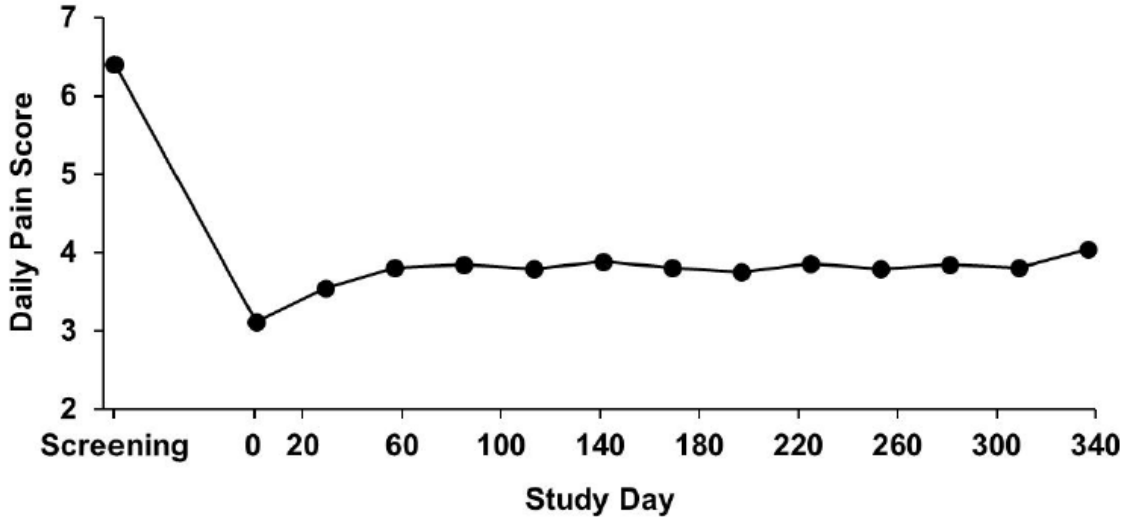
5.3.5 Efficacy Results – Study 802

Study 802 was designed as a long-term, open-label safety study. There were no prespecified primary or secondary efficacy endpoints. Efficacy data are presented qualitatively, with no claims of significance or comparative efficacy, but rather as supportive information to the efficacy results of Study 801.

5.3.5.1 Average Daily Pain Scores – Study 802

Subjects recorded their average daily pain scores using the 11-point NRS in a diary during the conversion/titration phase of the study, and their 24-hour NRS pain score was collected and recorded in the electronic case report form at each study visit. The mean of in-clinic NRS pain scores by study visit for subjects who entered the maintenance treatment phase of the study are displayed graphically in Figure 21. The pain score was reduced from a mean value of 6.4 at the time of study entry (Screening) to 3.1 after treatment with HC-ER in the conversion/titration phase of the study, qualitatively similar to the reduction seen in Study 801 (Table 13). Mean pain scores rose slightly by about 0.7 point during the early portion the maintenance treatment phase of the study, but remained stable from about Day 60 to the end of study.

Figure 21: Average Daily Pain Intensity Score (In-Clinic) by Visit, Subjects in the Maintenance Treatment Phase, Study 802



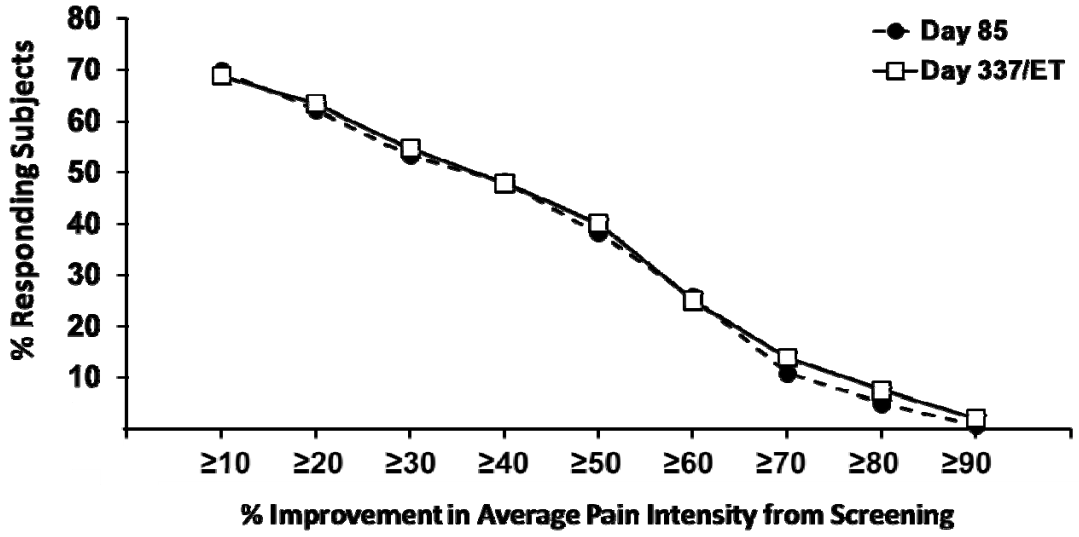
5.3.5.2 Responder Rate Analysis – Study 802

Response was defined as percent improvement in average pain intensity as measured in clinic by the 0-10 NRS from the Screening pain intensity score to the study visit of interest. Subjects who terminated early from the study were considered non-responders.

Figure 22 shows the proportion of subjects at either Day 85 or Day 337 (the last study visit). Day 85 was selected because it was the time of the last study visit assessed in Study 801.

Considering a response of ≥30% from Screening, 53% of the subjects were scored as responders at Day 85 and 55% were scored as responders at Day 337. Considering a response of ≥50% from Screening, 38% of the subjects were scored as responders at Day 85 and 40% were scored as responders at Day 337. A response rate of 30% is considered clinically meaningful (Dworkin 2009). These results appear qualitatively similar to the results of Study 801.

Figure 22: Response Rate – Subjects in the Maintenance Treatment Phase, Study 802

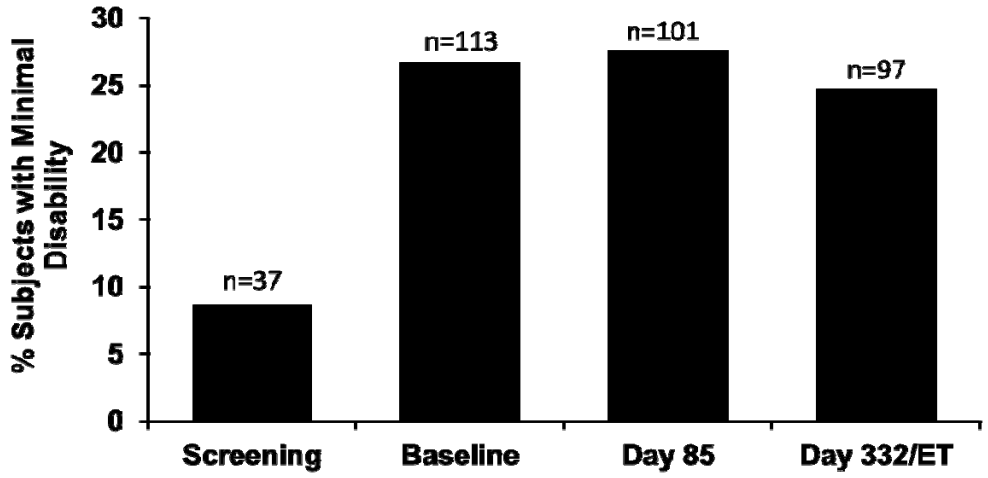


5.3.5.3 Oswestry Disability – Study 802

The ODI is based on answers to pain related questions (pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and traveling) which are tallied and a score from 0-100 is calculated. Minimal disability is generally considered as an ODI score less than 20. The ODI has been most extensively validated in patients with back pain, which was reported as a source of chronic pain in 40% of the subjects in Study 802.

For the subjects who entered the maintenance treatment phase of Study 802, only 9% had a Screening ODI score that indicated mild disability (Figure 23). After treatment with HC-ER in the conversion/titration phase of the study, which averaged 30 days in duration, the proportion of subjects with minimal disability on the ODI scale at Baseline increased to 27%. The effect appeared durable, as 28% of subjects at Day 85 and 25% of subjects at Day 337 (end of study) still scored as minimal disability on the ODI scale. This suggests a durable improvement in physical function for the subjects who completed the study.

Figure 23: Proportion of Subjects with Minimal Disability, Oswestry Scale– Subjects in the Maintenance Treatment Phase, Study 802



5.3.5.4 Subject Global Assessment of Medication

The SGAM addresses subject satisfaction with the current regimen of pain medication. Higher levels of subject-reported satisfaction indicate better pain management. At Screening, 73% of subjects enrolled in the maintenance treatment phase were at least moderately satisfied (at least at the midpoint of the satisfaction scale) with their current pain management regimen. At Baseline, after reaching a stabilized dose of HC-ER during the conversion/titration phase, the percentage of subjects who were at least moderately satisfied had increased to 99%. At the end of the study, 92% of subjects (361 of 392) remained at least moderately satisfied with treatment.

5.3.5.5 Hospital Anxiety and Depression Scale (HADS)

In a study such as 802, HADS testing is done primarily to exclude subjects with depression from entering the study, and to detect any negative impact of chronic opioid treatment on emotional functioning. Compared to the Screening values, there were small decreases in both anxiety and depression HADS scores after open-label conversion and titration of HC-ER (baseline) and after 48 weeks of maintenance treatment (end of study).

5.3.5.6 Brief Pain Inventory

The Brief Pain Intensity (BPI) questions used in this study were a combination of pain intensity and quality-of-life measures. The BPI showed treatment with HC-ER decreased pain intensity from Screening to Week 48 across the spectrum (least and worst in past 24 hours, average, and current) and increased mean percentage of pain relief from 55% to 69%. Reduced interference of pain in normal functioning was observed for all quality of life parameters.

5.3.5.7 Efficacy Conclusions – Study 802

Study 802 was designed as a long-term, open-label safety study. There were no prespecified primary or secondary efficacy endpoints. Qualitative efficacy data presented confirm the

efficacy data from pivotal study 801, and suggest that HC-ER exerted an effect of pain relief that was sustained over a year of maintenance therapy. The reduction in pain relief was accompanied by an increase in the proportion of subjects with disability in the minimal range as measured by the ODI, with no worsening of emotional function, and some suggestion of improved physical functioning.

5.3.6 Compliance – Study 802

HC-ER and rescue medicine (HC/APAP) were distributed in numbered bottles. Subjects were required to record every dose of study medication and rescue medication in a diary. At every visit, all medication bottles (empty, full or part-full) and the diary were reviewed. Returned study medication was counted and witnessed in front of the subject and logged with all three signatures. The study staff compared the medication counts to the diary entries and discussed them with the subject.

A compliance index was calculated by dividing the number of doses of study medication taken by the number of doses that were predicted based on the assigned dosing regimen, and expressed as a percentage. The proportion of subjects who had a compliance index above 90% in the maintenance treatment phase of Study 802 was 98%.

5.3.6.1 Drug Accountability – Study 802

Drug accountability data were analyzed to calculate the amount of missing drug, expressed as the amount of missing drug (units that should have been returned but were not) divided by the total number of units of drug that were dispensed during the study. Case report form data suggested that <4% of the total number of dispensed HC-ER capsules could be considered missing and <5% of the dispensed rescue HC/APAP tablets could be considered missing.

5.3.6.2 Investigation of Suspected Diversion - Study 802

A total of 66 subjects had drug accountability issues identified during Study 802. Thirty-two were in the conversion/titration phase of the study, and 33 were in the maintenance treatment phase of the study. In 30 of the 66 instances, the investigator and sponsor agreed that the accountability issue was plausibly an error or accident, and the subject was allowed to continue on study; the remaining 36 subjects were discontinued from the study for noncompliance.

The amount of study medication involved in the 66 drug accountability cases totaled 3,961 capsules of HC-ER and 1,486 tablets of HC/APAP. This represented 0.49% of the HC-ER dispensed over the course of the study, and 0.47% of the HC/APAP dispensed over the course of the study.

In addition, verbatim AE terms were searched for any evidence of abuse, misuse or overdose. One subject in Study 802 had a verbatim TEAE term of abuse, and 8 had a TEAE term of misuse. One subject had a verbatim term of overdose, a known case of attempted suicide which the subject survived.

There was one site level diversion during the course of Study 802. Drug accountability issues were identified during a routine monitoring visit and confirmed by an independent

for-cause audit. Errors, incomplete entries, improper study document corrections, and incidents of suspected falsification/reconstruction of study documents were discovered and attributed to the site's study coordinator. The site filed reports to the local authorities, the DEA and the State Board of Nursing. The site initiated re-training, enhanced drug accountabilities procedures, updated Standard Operating Procedure, and criminal background checks for all employees. Zogenix re-trained and re-qualified the site; Zogenix also replaced the clinical monitor and audited all other sites managed by the clinical monitor at the time of the diversion. The amount of study medication involved in this site's drug accountability case totaled 121 capsules of HC-ER and 176 tablets of HC/APAP.

5.4 Integrated Safety Analyses

The overall safety profile of HC-ER has been evaluated in 10 studies involving 1568 subjects representing a wide variety of populations, including healthy volunteers, subjects with renal and hepatic impairment patients, subjects with acute pain, and subjects with chronic pain. The six Phase 1 studies, the two Phase 2 studies and the two Phase 3 studies are described in Table 12.

The safety population that is most relevant to the current NDA application for HC-ER is the Chronic Pain population, which encompasses Study 801 and Study 802. The Chronic Pain population represents the most relevant population to the intended use of HC-ER and also provides the greatest exposure to HC-ER in terms of dose levels and duration. Therefore, safety data in this section are summarized for the combined Chronic Pain population comprised of integrated data from 801 and Study 802. Analyses of safety for an All Subjects database did not differ materially from the Chronic Pain analyses. Zogenix is not seeking an acute pain indication, but for completeness the safety results from the Phase 2 study in acute postoperative bunionectomy pain are summarized in Section 5.4.5.

5.4.1 Study Drug Exposure – Chronic Pain Population

Overall 1148 subjects received one or more doses of HC-ER in the integrated Chronic Pain population. Chronic pain patients were treated with individualized doses of HC-ER across a broad range of doses (20 - 600 mg TDD). The duration of HC-ER exposure ranged from 1 day to 12 months, with a total of 336 subjects treated for 6 months and 285 subjects treated for 1 year. The mean duration of HC-ER exposure in the Chronic Pain population was 30 days in the conversion/titration phase, and 77 days in Study 801 and 267 days in Study 802 in the treatment phase.

5.4.2 Treatment-Emergent Adverse Events – Chronic Pain Population

A summary of TEAEs occurring in ≥2% of the integrated Chronic Pain population and occurring in any phase of the studies (conversion/titration or maintenance treatment) is presented in Table 28. The most common TEAEs, occurring in greater than 5% of the integrated study subjects, were constipation (15.4%), nausea (13.4%), headache (8.3%), somnolence (7.8%), vomiting (7.1%), back pain (5.7%), and fatigue (5.1%). The majority of TEAEs in HC-ER-treated subjects were mild or moderate in intensity. The results are consistent with the previous analyses of safety data from Study 801 and 802. No new or

unexpected safety signals were detected from the analyses of the combined Chronic Pain dataset.

SAEs and deaths are discussed separately for Study 801 in Section 5.2.5.4 and for Study 802 in Section 5.3.4.4.2.

Table 28: Summary of TEAEs Experienced by ≥2% by Preferred Term, Chronic Pain Population

	Total (N=1148)
Number of Subjects with at least 1 event	859 (74.0%)
Constipation	177 (15.4%)
Nausea	154 (13.4%)
Headache	95 (8.3%)
Somnolence	89 (7.8%)
Vomiting	82 (7.1%)
Back pain	65 (5.7%)
Fatigue	58 (5.1%)
Insomnia	57 (5.0%)
Diarrhea	51 (4.4%)
Dizziness	49 (4.3%)
Arthralgia	47 (4.1%)
Upper respiratory tract infection	43 (3.7%)
Urinary tract infection	43 (3.7%)
Fall	42 (3.7%)
Nasopharyngitis	42 (3.7%)
Edema peripheral	39 (3.4%)
Muscle spasms	37 (3.2%)
Anxiety	36 (3.1%)
Sinusitis	36 (3.1%)
Bronchitis	34 (3.0%)
Dry mouth	32 (2.8%)
Depression	29 (2.5%)
Influenza	29 (2.5%)
Pruritus	29 (2.5%)
Pyrexia	29 (2.5%)
Pain in extremity	28 (2.4%)
Muscle strain	27 (2.4%)
Lethargy	25 (2.2%)
Abdominal pain	24 (2.1%)
Contusion	24 (2.1%)

5.4.3 TEAEs by Dose – Chronic Pain Population

The subjects in the Chronic Pain population were divided into two dosing groups, one whose modal dose (the most frequently received dose across the study) of HC-ER was less than 100 mg per day, and the other whose modal dose of HC-ER was ≥100 mg per day. A summary of TEAEs occurring in greater than 2% of the integrated Chronic Pain population and occurring in any phase of the studies by modal HC-ER dosage group is presented in Table 29.

Most TEAEs were similar in incidence in the low dose group (<100 mg HC-ER per day) and in the high dose group (≥100 mg HC-ER per day). There were no striking or unexpected differences between the two groups. In general, the most common TEAEs were similar across both dose groups. Some of the more common TEAEs were higher in the high dose group while others were higher in the low dose group. Statistical testing was not applied to this post-hoc analysis.

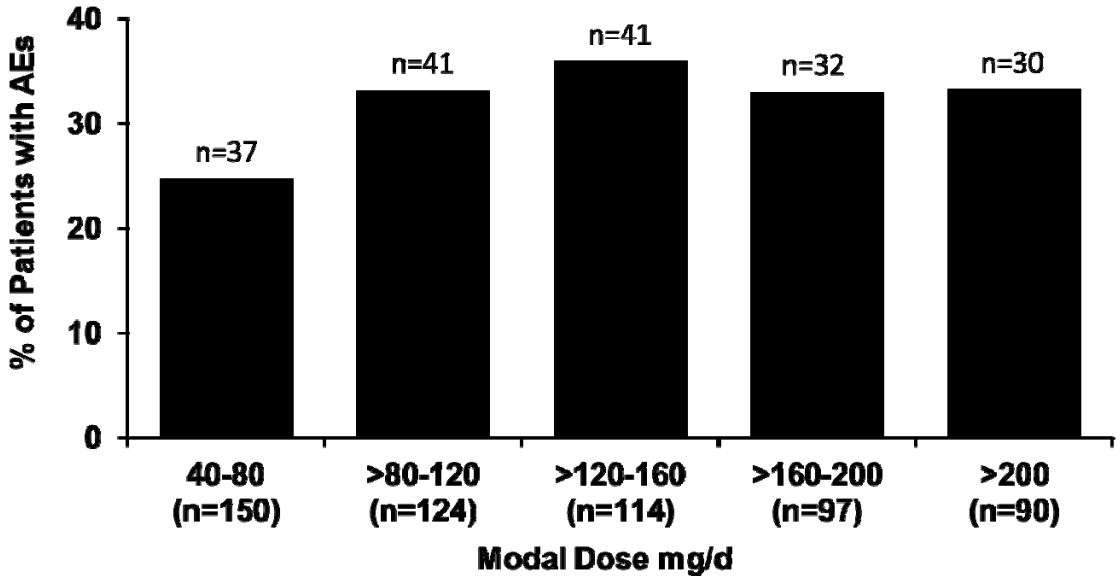
Table 29: TEAEs Experienced by ≥2% of Subjects by Preferred Term, by Modal Total Daily Dose - Chronic Pain Population

	HC-ER <100 mg Modal TDD (N=464)	HC-ER ≥100 mg Modal TDD (N=684)
Number of Subjects with at least 1 event	316 (68.1%)	533 (77.9%)
Constipation	58 (12.5%)	119 (17.4%)
Nausea	65 (14.0%)	89 (13.0%)
Vomiting	26 (5.6%)	56 (8.2%)
Back pain	10 (2.2%)	55 (8.0%)
Headache	41 (8.8%)	54 (7.9%)
Somnolence	39 (8.4%)	50 (7.3%)
Fatigue	20 (4.3%)	38 (5.6%)
Urinary tract infection	7 (1.5%)	36 (5.3%)
Insomnia	23 (5.0%)	34 (5.0%)
Arthralgia	14 (3.0%)	33 (4.8%)
Diarrhea	19 (4.1%)	32 (4.7%)
Fall	11 (2.4%)	31 (4.5%)
Nasopharyngitis	11 (2.4%)	31 (4.5%)
Upper respiratory tract infection	12 (2.6%)	31 (4.5%)
Edema peripheral	9 (1.9%)	30 (4.4%)
Dizziness	21 (4.5%)	28 (4.1%)
Anxiety	9 (1.9%)	27 (3.9%)
Bronchitis	7 (1.5%)	27 (3.9%)
Muscle spasms	10 (2.2%)	27 (3.9%)
Sinusitis	9 (1.9%)	27 (3.9%)
Influenza	6 (1.3%)	23 (3.4%)
Pyrexia	8 (1.7%)	21 (3.1%)
Muscle strain	7 (1.5%)	20 (2.9%)
Depression	10 (2.2%)	19 (2.8%)
Pain in extremity	9 (1.9%)	19 (2.8%)
Contusion	6 (1.3%)	18 (2.6%)
Gastroenteritis viral	3 (0.6%)	18 (2.6%)
Neck pain	4 (0.9%)	17 (2.5%)
Pruritis	12 (2.6%)	17 (2.5%)
Hot flush	3 (0.6%)	15 (2.2%)
Abdominal pain	10 (2.2%)	14 (2.0%)
Dry mouth	18 (3.9%)	14 (2.0%)
Migraine	3 (0.6%)	14 (2.0%)
Musculoskeletal pain	8 (1.7%)	14 (2.0%)
Pain	3 (0.6%)	14 (2.0%)
Lethargy	12 (2.6%)	13 (1.9%)
Pruritus allergic	11 (2.4%)	7 (1.0%)

A list of adverse event preferred terms commonly associated with opioid use was generated and included, e.g., nausea, constipation, vomiting, dry mouth, somnolence, headache, dizziness, sedation, fatigue, and pruritus. The percentages of subjects in the Chronic Pain population who experienced at least one of these adverse events during the maintenance treatment phase were tabulated by modal dose of HC-ER. As shown in Figure 24, there was

a slight increase in the proportion of subjects with these opioid adverse events up to a modal dose of 80-120 mg HC-ER per day, but no substantial increase in these common opioid-associated adverse events above 120 mg HC-ER per day, including doses above 200 mg HC-ER per day.

Figure 24: Proportion of Subjects Experiencing Adverse Events Commonly Associated with Opioid Use during Maintenance Treatment, Chronic Pain Population



5.4.4 Long-term Safety

A total of 336 subjects received HC-ER treatment for at least 6 months and 285 subjects were treated for up to one year. The high completion rate (67%) for subjects in Study 802 suggests that subjects were able to effectively manage adverse events, in some instances with dose modification, in manner that provided good overall tolerability.

Subjects in the Chronic Pain population who received HC-ER in the maintenance treatment phase for at least 45 days were analyzed to explore the safety profile of HC-ER during long-term exposure. Late-onset TEAEs were defined as any AE that occurred for the first time after a subject had been exposed to HC-ER for at least 45 days.

A total of 53.5% of HC-ER group subjects in the Chronic Pain population experienced at least one late-onset TEAE. Frequent TEAEs were back pain (9.2%), constipation (7.6%), vomiting (6.4%), arthralgia for (6.2%), and nausea (5.1%). No other late-onset TEAE was reported for ≥5% of subjects. Late-onset TEAEs did not appear to increase in incidence between 45 days and one year of HC-ER treatment.

5.4.5 Acute Pain Study– Safety Summary

There was a single study of HC-ER in subjects with acute pain conducted by the previous sponsor of the product. Study ELN-154088-201 was a randomized Phase 2 study of HC-ER PK, safety and efficacy in subjects following bunionectomy surgery. A total of 241 subjects received a single post-operative oral dose of HC-ER 10 mg (40 subjects), HC-ER 20 mg (40 subjects), HC-ER 30 mg (39 subjects), HC-ER 40 mg (40 subjects), hydrocodone 10 mg/APAP 325 mg (41 subjects), or placebo (41 subjects). There were no deaths or SAEs. One subject in the HC-ER 40 mg group discontinued because of an AE (abdominal pain, nausea, and pruritus). The incidence of nausea was 22.5%, 37.5%, 46.2%, and 55.5% in the HC-ER 10 mg, 20 mg, 30 mg, and 40 mg groups, respectively; 39.0% in the HC 10 mg/APAP 325 mg group, and 7.3% in the placebo group. The incidence of vomiting was 5.0%, 15.0%, 30.8%, and 30.0% in the HC-ER 10 mg, 20 mg, 30 mg, and 40 mg groups, respectively; 12.2% in the HC 10 mg/APAP 325 mg group, and 0% in the placebo group.

5.4.6 Safety Conclusions – Integrated Safety Analyses

Analyses of safety data pooled for Phase 3 studies 801 and 801 confirmed the safety conclusions of the two individual studies. HC-ER was generally safe and well tolerated, with a safety profile qualitatively similar to that of either immediate-release hydrocodone and of other ER opioid products. There were no new or unexpected safety issues revealed, and no indication that HC-ER carries a substantially different risk of any particular AE. The AE profile of HC-ER is similar at the highest doses studied to that with intermediate doses of HC-ER. As expected, there is some evidence of a dose effect for AEs between low doses of hydrocodone (20-40 mg per day) and intermediate doses (80-120 mg), but the latter overlaps with hydrocodone doses that are likely to be taken when patients with chronic pain increase their daily dose of HC/APAP because of developing tolerance. Overall, the frequency, type, and intensity of the adverse events for HC-ER were consistent across dose level and dosing duration ranges.

5.5 Clinical Conclusions

The efficacy of HC-ER compared to placebo was robust across a variety of standard methods for examining pain intensity in clinical trials. HC-ER was superior to placebo in relieving pain on group mean difference in pain intensity (average daily pain intensity scores—the primary study endpoint, $p=0.008$), and on measures of clinically meaningful individual improvement in pain intensity (30% response rate ($p<0.001$) and 50% response rate ($p<0.001$), which are considered “clinically important” and “major” improvement, respectively). In addition, subjects on HC-ER had a significantly longer time-to-exit due to loss of efficacy compared to placebo ($p<0.001$), which is an important and statistically powerful measure of analgesic efficacy. There was also evidence of efficacy in each of the additional domains that can demonstrate chronic pain treatment efficacy and effectiveness, when comparing HC-ER to placebo: physical functioning (lower disability scores, $p=0.026$), emotional functioning (lower depression scores, $p=0.006$), and participant ratings of global improvement (greater satisfaction with study medication, $p<0.001$).

HC-ER was generally safe and well tolerated, with a safety profile qualitatively similar to that of either immediate-release hydrocodone and of other ER opioid products. There were

no new or unexpected safety issues revealed, and no indication that HC-ER carries a substantially different risk of any particular adverse event.

6 RISK EVALUATION AND MITIGATION AND THE ZOHYDRO ER SAFE USE INITIATIVE

6.1 Introduction and Overview

In the last two years the federal government has developed broad initiatives to curb the increase in opioid abuse. In 2011 the Office of National Drug Control Policy issued a plan to curb opioid abuse that addresses initiatives for education, monitoring, proper medication disposal and enforcement. Additionally, FDA has recently approved a class-wide REMS for ER/LA opioid analgesics that is directed primarily towards providing training for prescribers. However, the problem of opioid abuse, misuse, and diversion still persists, and will require these new federal efforts and as well as additional risk mitigation efforts from industry and the private sector to impact the abuse and diversion of opioids.

Recognizing that the introduction of the first single-entity hydrocodone at higher unit doses than current hydrocodone combination products due to its 12-hour ER formulation could raise new concerns, Zogenix is committed to implementing risk mitigation and commercialization strategies in a responsible manner to address the specific risks posed by Zohydro ER with the goals of achieving safe and appropriate use for people with moderate to severe chronic pain.

Upon approval of the NDA, the commercialization of Zohydro ER and the implementation of the risk mitigation program will be the responsibility of Zogenix. Zogenix will introduce Zohydro ER into the market with a specific strategy intended to focus efforts only on clinicians who are familiar with prescribing extended release opioids for the management of chronic pain. However, anticipating that Zohydro ER may be prescribed outside of the targeted prescriber audience, Zogenix will identify and contact any such prescribers via Medical Affairs / Medical Information to ensure they have access to the necessary product information, educational resources, and Zohydro ER safe use initiatives to appropriately manage moderate to severe chronic pain with Zohydro ER. If it is determined that Zohydro ER is being prescribed inappropriately, the prescriber will be contacted by Zogenix to discourage further inappropriate use of Zohydro ER.

In addition to a responsible commercialization plan, Zogenix is committed to exceed the basic requirements of the recently established, class-wide REMS for ER/LA opioids in two important areas: 1) broad, yet focused educational initiatives on safe use and, 2) vigilant oversight of use and abuse patterns. Acknowledging that FDA and DEA mandated elements alone have not proven completely effective in preventing misuse, abuse and diversion of opioid analgesics, Zogenix is committed to evaluating interventions where there is potential for improved risk mitigation. The overall risk mitigation plan is designed to ensure that prescribers, pharmacists and patients understand the benefit-risk profile and responsible use and handling of Zohydro ER, and that Zogenix is closely monitoring the environment

through a battery of surveillance tools to rapidly detect and respond to concerning signals of abuse, misuse, or diversion.

6.2 Potential Risks Associated with Zohydro ER

There were 131 million prescriptions for hydrocodone combination products in 2011. The broad pain indication in the prescribing information, the convenience of writing a Schedule III prescription, coupled with the ability to request automatic refills have likely contributed to the situation where hydrocodone combination product availability is wide spread. As the most widely prescribed opioid, it is not surprising that hydrocodone consistently ranks highest in absolute rates of non-medical use of pain drugs. However, hydrocodone (relative) abuse ranks lowest among all prescription opioid drugs when adjusted for the number of prescriptions (Butler 2010). The oral abuse likability of pure hydrocodone has been shown to be less than hydromorphone and approximately the same as oxycodone (Walsh 2008). A study of the abuse potential and relative potencies of intravenous oxycodone, hydrocodone and morphine indicated significant abuse potential of all three compounds, and showed a rank order of potency: oxycodone > morphine > hydrocodone (Stoops 2010). In a recent systematic review of nine placebo-controlled likeability studies involving a comparison of hydrocodone and oxycodone relative to each other and/or of either one to morphine, it was concluded that oral hydrocodone has a reduced abuse liability compared to oral oxycodone (Wightman 2012).

Hydrocodone is a full mu opioid agonist and therefore the primary risks of Zohydro ER are the same as seen with other opioid drugs and the current hydrocodone combination products, namely overdose, misuse, abuse, and diversion. The risk mitigation initiatives for Zohydro ER will also take into consideration the current pattern of wide-spread, non-medical use of hydrocodone (in combination tablets) and ensure that the availability of Zohydro ER does not exacerbate the problem. In developing the safe use strategy for Zohydro ER, Zogenix has considered the potential for specific risks that may be associated with the first introduction of an ER single-entity hydrocodone product: in particular that Zohydro ER will be introduced in higher hydrocodone unit doses than available previously with the combination products. These higher unit doses reflect the needs of chronic pain patients as demonstrated in our clinical trial data.

While there are potential new risks associated with the introduction of Zohydro ER, as outlined above, the public health risk associated with this new formulation of hydrocodone will likely be similar to other ER/LA opioid analgesics. Zogenix is committed to commercializing the product in a manner that mitigates the risks of abuse, misuse and diversion of Zohydro ER, and to be vigilant in addressing any signals that arise.

6.3 Commercialization Plan

Zogenix is committed to commercializing Zohydro ER in a responsible manner with the goals of achieving safe and appropriate use for people with moderate to severe chronic pain. Zogenix will introduce Zohydro ER into the market with a specific strategy intended to focus efforts only on clinicians who are familiar with prescribing extended release opioids for the management of chronic pain, as these prescribers are more likely to appreciate the risks of

abuse and misuse, and more likely to seek and use education and pain management tools to support their practice.

FDA estimates there are 1.4 million DEA Schedule II and Schedule III registered prescribers. Of those, approximately 330,000 have written a prescription for a Schedule II ER opioid within the last year (Source: Source Healthcare Analytics, Source ® PHAST Prescription Monthly, September 2011 – August 2012). Zogenix is planning a sales effort which will focus on a targeted group of physicians comprising less than 15% of the 330,000 Schedule II ER opioid prescribers, therefore, minimizing risks associated with the inappropriate prescribing and use of Zohydro ER. This target group will be formally reviewed and approved by Company management at launch and on an ongoing basis – and clinicians identified as inappropriately prescribing Zohydro ER will be removed from the targeted group. Zogenix sales professionals will be compensated on specific goals related to their support of Zogenix' safe use initiatives including the educational elements in the REMS. Additionally, the sales-related portion of their incentive compensation will be capped, and be based only on prescriptions written by this approved group of prescribers. Specifically, Zogenix sales representatives will not be compensated for Zohydro ER prescriptions written by clinicians who have only written prescriptions for immediate release opioids. Other product promotional efforts will focus exclusively on scientific meetings and media dedicated to pain management. General primary care congresses and journals will not be part of the promotional strategy.

If Zogenix identifies healthcare professionals who are prescribing Zohydro ER who are not within the targeted promotional efforts, Zogenix will contact these prescribers via Medical Affairs/ Medical Information to ensure they have access to the necessary product information, educational resources, and Zohydro ER safe use initiatives to appropriately manage moderate to severe chronic pain with Zohydro ER. If it is determined that Zohydro ER is being prescribed inappropriately, the prescriber will be contacted by Zogenix to discourage further inappropriate use of Zohydro ER.

All Zogenix sales professionals engaged in the promotion of Zohydro ER will receive mandatory product and compliance training prior to launch and periodically thereafter as required by Zogenix. It is the policy of Zogenix that all U.S. commercial operations, promotion and medical education practices are executed in a consistent manner and in compliance with all applicable laws and regulations, including but not limited to relevant industry guidelines such as the American Medical Association Guidelines on Gifts to Physicians from Industry and the Pharmaceuticals Research and manufacturers of America (PhRMA) Code on Interactions with Healthcare Professionals. Any sales representative or employee determined not to be in compliance with company policies would be subject to disciplinary action up to and including termination. Ongoing compliance audits will be conducted by company personnel outside of the commercial organization or an appropriate third party.

6.3.1 Proposed Dosage Units of Zohydro ER

The clinical development program for Zohydro ER studied capsule strengths ranging from 10 mg to 50 mg hydrocodone. The pivotal efficacy study (Study 801) demonstrated that

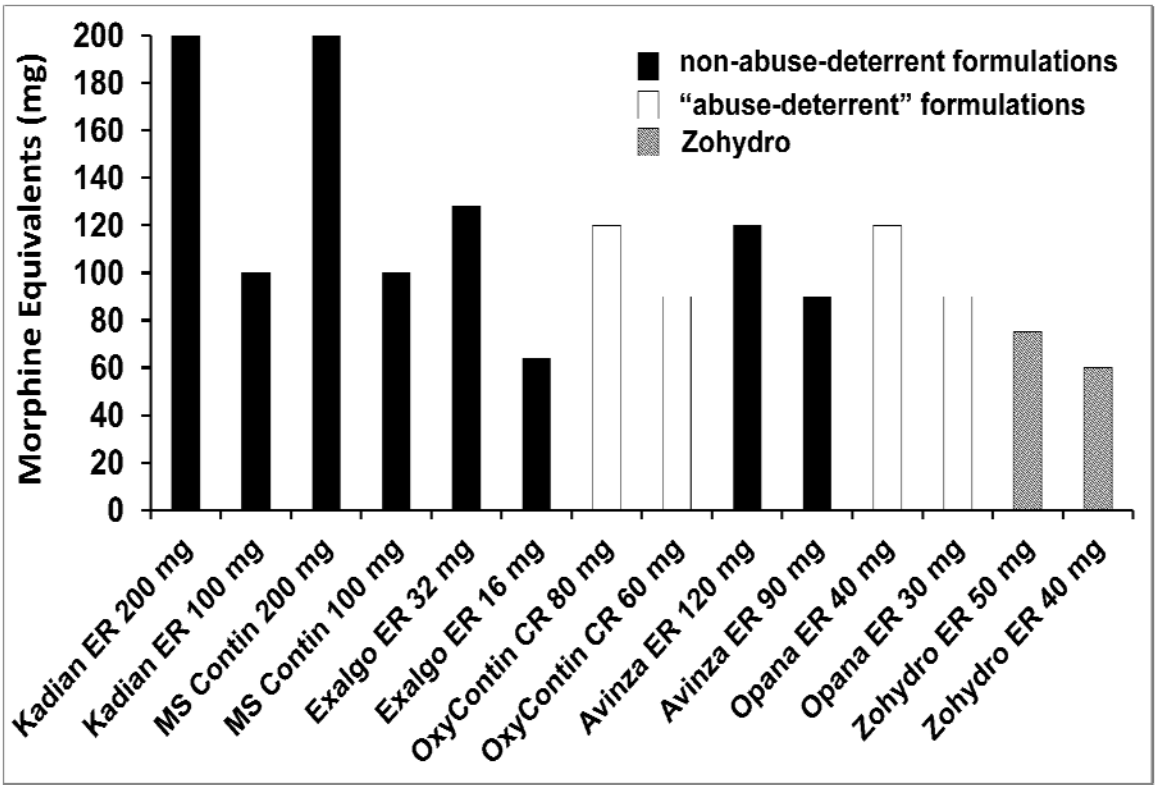
Zohydro ER was effective and well tolerated across a broad range of doses utilizing all dosage strengths (10 – 50 mg) of Zohydro ER and provided a beneficial treatment for patients with chronic pain.

As with the majority of approved ER opioid products, Zohydro ER does not have deliberate abuse-deterrent properties incorporated into the formulation. Achieving an effective abuse deterrent formulation is an ongoing objective for the industry and is a priority for Zogenix in our development program. Zogenix strongly supports the efforts made by manufacturers to develop and market new formulations of ER opioids, but also recognizes the challenges and potential limitations of abuse deterrent formulations. Current evidence suggests that an abuse deterrent formulation may change the route of product abuse and reduces, but does not eliminate abuse and misuse (Butler, NAVIPPRO Conf, 2012). Additionally, some suboptimal clinical experiences have arisen, such as, problems with swallowing (FDA Drug Safety website) and lack of or reduced efficacy within the appropriate patient population. Zogenix has an ongoing program to develop a meaningful abuse deterrent formulation of Zohydro ER in line with our commitment to safe use and FDA's desire to make this a priority for ER opioids.

Recognizing that Zohydro ER could be the first single-entity formulation of hydrocodone introduced into the market, consideration was given to limiting the dosage strengths at the initial launch. For example, the introduction of Exalgo (hydromorphone ER) followed this path. However, in considering the rationale for reducing the maximum strength (e.g., potentially reducing the risk of overdose) versus the clear benefit of higher strengths for patients who need higher dosage strength to control pain, Zogenix concluded the benefit outweighs the risk. Furthermore, the dose ranges of other ER opioids support the patient need for higher dosage strengths and the proposed 10 – 50 mg dose range for Zohydro ER. The highest proposed marketed dosage strength of Zohydro ER (on a morphine equivalent basis) is less than the upper doses of marketed formulations of all other available ER opioids (Figure 25) whether or not the products have abuse deterrent formulations.

Based upon the medical need in facilitating safe and effective dose escalation in patients with chronic pain, and supported by available dosage strengths across the class, Zogenix believes the net benefit is in favor of dosage strengths up to 50 mg. However, if the Advisory Committee and FDA view the benefit-risk of the 50 mg dose differently, Zogenix would be willing to voluntarily withhold this dose at launch, and reevaluate the introduction of the 50 mg dosage strength after the real-world benefit-risk profile is established.

Figure 25: A comparison of 40 and 50 mg strengths of Zohydro ER with the Two Highest Marketed Doses of Extended-Release formulations of Full mu Opioid Agonists by Morphine Equivalents



6.4 Risk Mitigation Program

Reducing serious negative outcomes, while maintaining patient access is a major legal, regulatory, industry and societal issue. Regulatory measures that are expected to reduce risk include DEA Schedule II prescribing status, and participation in the FDA's ER/LA opioid REMS education program.

In this context, Zogenix is committed to undertaking a comprehensive risk mitigation program of mandated elements supplemented by both internal and external tools and programs to:

- provide surveillance of aberrant drug-related behaviors involving Zohydro
- facilitate responsible prescribing of Zohydro by targeted, current ER/LA opioid prescribers
- educate all stakeholders – prescribers, patients, and pharmacies
- pilot innovative programs linking patient assessments to prescriber tools for managing patients on Zohydro
- assess the effectiveness of these programs under its Zohydro Safe Use Initiative program, including review by an independent Safe Use Advisory Board.

These programs are listed in Table 30. The elements listed under the column "ER/LA Opioid REMS" are those REMS elements mandated by FDA (described below), whereas those

elements listed under "Zohydro ER Safe Use Initiatives" are additional intervention and prevention tools, and surveillance systems that are efforts beyond the FDA mandated REMS that Zogenix will use to monitor and evaluate the safe use of Zohydro ER. As described in detail below, several of these novel programs will be piloted and evaluated regionally to assess which initiatives are the most effective and should be expanded nationally. Results of all research will be shared with both public agencies and industry with the goal of identifying tools which can be expanded to improve risk mitigation efforts for other opioids.

Table 30: Risk Mitigation Elements of the ER/LA Opioid REMS and the Zohydro ER Safe Use Initiative

	ER/LA Opioid REMS	Zohydro ER Safe Use Initiative
Patient Initiatives	● Medication Guide ● Counseling	● Patient Treatment Kit ● Web-based and print education (painACTION) ● Opioid disposal program ● Locking bottle cap / lock box
Prescriber Initiatives	● REMS education ● Safe use training ● Risk training	● Targeted prescriber marketing ● Prescriber training and education, including mentoring ● Prescriber tool kit ● Patient selection tools ● Urine drug screening ● Web-based and print education (PainEDU & MAP-PC) ● Clinical tools (painCAS, SOAPP and COMM)
Pharmacist Initiatives		● Pharmacist brochure ● Web-based and print education (PainEDU)
Distributor Initiatives		● Distributor Starter Kit
Assessments	● Prescriber training ● Quality of materials ● HCP awareness ● Patient risk understanding ● Misuse, abuse, overdose, addiction, death rates ● Utilization patterns ● Prescribing behaviors ● Prescribing patterns	● Surveillance for medical and non-medical use ● Teenager surveillance ● Internet and media surveillance ● Safe Use Advisory Board ● Cash claim data ● Pharmacovigilance review

6.5 Required Risk Mitigation Elements

This section describes those risk mitigation elements that are required by FDA or DEA. These include product DEA scheduling, prescribing information (product labeling), and the recent FDA-approved REMS for ER/LA opioid analgesics.

6.5.1 DEA Scheduling

Exemptions in DEA drug scheduling allow low dosage strengths (i.e., less than 15 mg) of hydrocodone, when combined with a non-opioid analgesic such as acetaminophen or

ibuprofen, to exist as DEA Schedule III drug products. As Zohydro ER is a single-entity product, developed for dosage strengths greater than 15 mg and not combined with a non-opioid analgesic, this will be the first hydrocodone product available as DEA Schedule II.

There are significant differences between DEA Schedule II and III products, including how the products can be prescribed, amount of product, refills, and whether covered by the FDA mandated REMS. These differences are summarized in Table 31.

Table 31: Prescription Differences Between Schedule II and Schedule III Drugs

	Schedule II	Schedule III
Rx can be called into pharmacy	No	Yes
Automatic RX refills allowed	No	Yes
Tracked by Prescription Drug Monitoring Programs	Yes	Some
Ordered, inventoried and dispensed differently by pharmacies	Yes	No
FDA mandated REMS	Yes	No

6.5.2 Product Labeling

The Zohydro ER product labeling (package insert) contains opioid analgesic class labeling and specifies information about mitigating the risks of overdose, abuse and diversion. These are described below

6.5.2.1 Class Labeling

Recognizing the abuse and misuse potential of an ER hydrocodone product that will be available in higher dosage strengths than current combination hydrocodone products, the Zohydro ER package insert will contain class-labeling elements that are common to all ER/LA opioid analgesics. This includes the indication statement (indicated for the management of moderate-to-severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time), Boxed Warnings, Warnings and Precaution statements, and alcohol interactions.

6.5.2.2 Accidental Overdose

Patients will be instructed to take Zohydro ER exactly as prescribed, including taking no more than their prescribed dose of Zohydro ER. The labeling contains recommendations on assessing patients before initiation of therapy, opioid conversion ratios, and other precautions including avoiding the consumption of alcohol. Patients will be instructed to avoid drinking alcohol while taking Zohydro ER, both because the CNS depressive effects of opioids and alcohol are at least additive, and because consuming Zohydro ER with alcohol can potentially circumvent the ER technology leading to an increase in blood levels of hydrocodone and adverse effects.

6.5.2.3 Abuse, Misuse and Diversion

Prescribers will be instructed to use caution in prescribing Zohydro ER to patients who may be at risk for abuse, misuse and diversion. Patients should be assessed for their clinical risks for opioid abuse, misuse, or addiction before being prescribed Zohydro ER. As required for all patients who are prescribed Schedule II pain medications, patients receiving Zohydro ER should be routinely monitored for signs of misuse, abuse, and addiction. In addition to screening, prescribers will be instructed and encouraged to employ best practices in management of pain in patients taking Zohydro ER. This will include triaging of patients according to risk factors, stratifying patients according to risk category, initiating treatment strategies that match the risk category, and monitoring patients and changing the treatment strategy if they move from one risk category to another. Zogenix will provide prescribers with a suite of tools (see Section 6.6.1) at no cost to assist in proper patient selection and on-going patient management

6.5.3 ER/LA Opioid Analgesics REMS Program

On July 9, 2012, FDA approved a class-wide REMS for ER/LA opioid analgesic products. The ER/LA opioid analgesic REMS applies to 15 NDA and ANDA manufacturers with ER or LA opioid products, numbering approximately 30 distinct opioid analgesic products, and includes a shared implementation program. However, each ER/LA opioid product manufacturer must individually submit the (same) REMS for approval by FDA. It is within this framework that Zogenix submitted a REMS for Zohydro ER in the submitted NDA. The presentation of the ER/LA opioid REMS as submitted to the Zohydro ER NDA is appended as Appendix 5.

The goal of the FDA-approved opioid REMS (as well as the Zohydro ER REMS) is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of ER and LA opioids (collectively referred to as ER/LA opioids) while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

The FDA approved REMS consists of a Medication Guide, elements to assure safe use (ETASU), and a timetable for submission of assessments. The ETASU include a CME-based education program for prescribers, and patient education materials that include a Medication Guide and information on how to properly take an opioid, report adverse effects, and store opioids. The timetable for submission of REMS assessments is six months, 12 months, and annually after the NDA is approved. Assessments include: the number of prescribers having completed the education program; an independent audit of the quality of the education materials used to train prescribers; an evaluation of patient and prescriber awareness of the risks associated with ER opioids; a surveillance plan to monitor misuse and abuse of opioids, including surveillance in various risk groups and settings; and evaluations of drug utilization and prescribing behaviors. The FDA recommended that the sponsors of ER opioids cooperate to establish a single system for monitoring these assessments across all ER opioid products.

6.5.4 Zohydro ER REMS

Zogenix is a member of the REMS Program Companies, or RPC, developing materials to inform and educate healthcare professionals on safe prescribing practices, and includes patient counseling about the risks of ER/LA opioids. The REMS submitted in the Zohydro ER NDA is identical to the REMS for all the other class members.

The major components of the Zohydro ER REMS program include the following:

- A Medication Guide for Zohydro ER (Appendix 3).
- Training for prescribers of ER/LA opioid analgesics, including Zohydro ER.
- Information that prescribers can use to educate patients about the risks of ER/LA opioid analgesics and their safe use, storage and disposal (Patient Counseling Document [Appendix 4]).
- Information for prescribers about the existence of the Zohydro ER REMS (Appendix 5) and the need to successfully complete the necessary training.

6.6 The Zohydro ER Safe Use Initiative

Zogenix acknowledges that additional efforts beyond the recent FDA mandated REMS and prescribing information, and DEA scheduling will be required to ensure the safe use of Zohydro ER. Despite large expenditures of time, effort and funds by both government and private organizations, the public health consequences of overdose and death from opioids remain high (15,000 opioid related deaths last year; CDC.gov). Clearly more has to be done in this area in order to further diminish the risks of these products without compromising the benefit for pain patients. Zogenix has taken the position that more can be done to ensure the safe use of opioids, and therefore we are committed to developing and testing interventions or prevention programs where there is potential evidence for usefulness. The safe-use initiatives build upon the mandated elements of the REMS by addressing gaps in the standard REMS. Zogenix, working with experts on opioid abuse and risk mitigation, will be the first ER opioid manufacturer to introduce a comprehensive, forward looking program to supplement the mandated REMS. The plan leverages both existing tools demonstrated to reduce abuse risk, along with innovative new initiatives that will help advance risk surveillance and mitigation knowledge and practice going forward.

Zogenix intends to initiate and test several innovative programs. These pilot initiatives include painCAS and MAP-PC described below, as part of the NAVIPPRO intervention and prevention programs. These will be launched in 2013, and assessed regionally on a pilot basis to assess effectiveness. If they prove successful, they will be scaled up and offered to all prescribers. Other programs exist today, and will be launched more broadly.

6.6.1 Leveraging Existing Tools to Augment Intervention and Education

Zogenix is proposing to partner with Inflexxion®, a research and contract research organization with approximately 25 years of experience, to provide state of the art research programs and technologies to help ensure appropriate and safe management of patients on opioid analgesic therapy with Zohydro ER. Inflexxion is a separate corporate entity, and has no financial interest in either Zogenix or Zohydro ER.

Inflexxion began development of the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) in 2001 with a grant from National Institutes of Drug Abuse (NIDA). This enabled the development of an integrated suite of tools, programs and technologies that have become the foundation of the NAVIPPRO system. The system is comprised of two main components:

1. a set of intervention and prevention tools and resources that support education through mentoring, skill building, simulations, and provision of clinical relevant information for healthcare providers and patients
2. a group of tools and assessments that provide surveillance of the landscape of aberrant drug-related behaviors involving opioids (discussed in Section 6.6.4.1)

The NAVIPPRO tools include both intervention and prevention programs such as the Pain Assessment Interview Network – Clinical Advisory System (painCAS®), PainEDU®, painACTION®, and Managing Addiction and Pain in Primary Care (MAP-PC®), as well as surveillance tools (discussed in Section 6.6.4.1). Moreover, these tools should be viewed as an integrated suite instead of individual and isolated elements, as the tools allow, for example, information to flow between prescribers and patients which encourages increased communication and better management of patients taking ER/LA opioid products. It is important to note that considerable NIH or NIDA funding supported the development and testing of each of these programs. And there is extensive literature in referenced journals supporting the scientific validity of these programs (e.g. Butler 2004; Butler 2008; Butler 2009; Butler 2010; Chiauzzi 2010; Bromberg 2012).

The NAVIPPRO tools will augment the standard class-wide ER/LA REMS for Zohydro ER that focuses primarily on voluntary healthcare provider education, and secondarily on education of the patient (e.g., Medication Guide and Patient Counseling Document) regarding the risks and benefits of these opioids. The REMS Program Companies-sponsored continuing education training for prescribers will be a one-time event of approximately 3 hours in duration. Completion of the CE and examination will only demonstrate knowledge acquisition of the program content, and not whether it has impacted how prescribers actually practice (e.g., select appropriate patients or how to manage them over time). NAVIPPRO's intervention and prevention program is a more comprehensive program that facilitates, motivates, and encourages education and the longitudinal interaction (behaviors) of prescribers and patients that would be more beneficial and successful in addressing opioid misuse, abuse, and diversion.

Additionally, Zogenix will commission Inflexxion to use its expertise to initiate research with the goal of identifying methodologies and strategies for increased program engagement with respect to voluntary pain education among healthcare providers, and is committed to going to whatever lengths necessary to this specific subject.

The specific NAVIPPRO educational and interventional tools, and the issues they address, are shown in Table 32.

Table 32: NAVIPPRO Educational and Interventional Tools Being Used to Address Practice Gaps not Covered by the Class-Wide ER/LA Opioid REMS

Practice Gap	Tool	Description	What it will accomplish
Prescribers and Pharmacists: • Educational deficits • Where to access educational resources and information on pain management • Lack of access to print or online educational materials	PainEDU	Online and hard-copy non-promotional comprehensive pain education resources. Over 50,000 registered users, and increasing by > 1,000/month	1) Provides guidance and evidenced-based information on patient assessment, appropriate patient selection, use of opioid risk assessment tools in clinical practice, case studies, formulation of treatment plans and monitoring along the course of therapy. 2) A tool to reduce inappropriate prescribing.
Patients: • Lack of trusted non-promotional resources and knowledge about chronic pain management	painACTION	NIH-funded efficacy-tested, web-based self management solution designed to educate and empower people with chronic pain. Provides interactive features, tools, and learning modules to help patients manage specific types of pain.	1) Provides up-to-date resources and knowledge about important topics to chronic pain patients and caregivers. 2) Provides literacy-level appropriate information and education on medication safety courses, including topics such as proper use, storage, and disposal of opioids.
Prescribers: • Pain management assessments not standardized • Longitudinal assessments not conducted nor available • (Graphical) reports for prescriber & patient not available	painCAS	NIH funded painCAS contains standardized electronic format assessments that are completed the patient and include the "gold standard opioid risk assessment tools SOAPP and COMM. Provide an organized and standardized clinical plan/report for prescribers & patients.	1) Assessments are standardized to reduce clinician variability; the tools help clinicians assess and stratify risk of aberrant drug-related behaviors, on an on-going basis. 2) Provides information to prescriber for tracking quality improvement and treatment outcomes. 3) Allows patients to complete assessments remotely (more efficient for prescribers & patients). 4) Directs patients to painACTION for relevant education 5) Directs HCPs to PainEDU for relevant education 6) Tool to reduce inappropriate prescribing, and detection of patients at increased risk of abuse and misuse
Prescribers: • Resource for acquiring skill sets and knowledge to manage patients at increased risk of opioid abuse and misuse	MAP-PC	NIH funded standardized-patient simulated educational program to assist clinicians acquire the skill sets and knowledge on identification, management, treatment, and pain patient referral, through an engaging and virtual simulation and immersive interactive platform.	1) Assists prescribers to make informed decisions about prescribing opioids in complex situations. 2) Has measures that allow for assessments of behavioral change, motivation, and intention to incorporate learning into clinical practice.

PainEDU and PainACTION are available for use now, and will be made available to all Zohydro ER prescribers. MAP-PC and painCAS are undergoing testing, will be available in 2013, and would be pilot tested regionally for evaluation prior to a nation-wide launch.

6.6.1.1 PainCAS

PainCAS is the central hub of the NAVIPPRO programs (Figure 26) with the following features. It is a program that aims to improve the quality of pain assessment and treatment through the use of a standardized and comprehensive tool that can be used to positively impact how pain assessment and management is conducted. Taking the standard pain assessment from a paper and pencil to an electronic format, this program streamlines and facilitates the clinical process by using initial and follow-up assessments that allow for standardization of practice and outcomes assessment. These assessments include the nationally recognized and validated opioid risk assessment tools, including the Screener and Opioid Assessment for Patients with Pain (SOAPP) and the Current Opioid Misuse Measure (COMM). Developed with support from the NIDA, SOAPP helps clinicians assess and stratify risk of aberrant drug-related behaviors, as well as guiding the clinician with respect to appropriate monitoring and management. The COMM was also developed with NIH funding, and is a corresponding patient self-report measure of risk for aberrant drug-related behavior among patients with chronic pain who are prescribed opioids for pain along the continuum of therapy. It was developed to complement SOAPP's predictive screening of opioid misuse potential and improve a clinician's ability to periodically assess a patient's risk for opioid misuse on an ongoing basis.

Figure 26: Synergistic Relationship of NAVIPPRO Tools

PainCAS includes a set of standard assessment questions for the pain patient. The questions and answers are collected as individual data elements, and provided to the prescriber as an (at a glance) report, also containing pertinent positive information, and also containing the

answers to all of the individual assessment questions. The additional the value of PainCAS is that it standardizes these assessments reduces clinician variability, and has the ability to measure an improved quality of care, while providing clinical guidance to clinicians based on evidence-based guidelines and practice recommendations.

As the interaction is via electronic media, the information can be captured longitudinally and included in on-going reports to be used by both the prescriber and patient. For example, the patient completes an initial assessment, which is provided to the prescriber as an initial assessment report. Follow-up reports can be integrated with the initial report, and the prescriber can view graphical output of pain ratings and COMM scores. This information can be useful to the prescriber for tracking quality improvement and treatment outcomes. The patient report, similar in format to the provider follow-up report, can also depict graphical pain and functional assessments, keeps a patient informed and involved in treatment, and furthermore directs them to the painACTION.com website for educational pain self-management (see below). Therefore, another value proposition of PainCAS is that there is continued monitoring of the patient by the prescriber, and this continued patient management is important to ensure that patients continue to need the product, are using the product correctly, and they are not seeking the product for diversion purposes.

In summary, painCAS provides window into clinical practice, along with an organized and standardized clinical roadmap for both prescribers and patients, minimizing the likelihood of miscommunication or deficits in care. For prescribers, it captures pain and risk assessments, provides decision support and data analysis, summarizes diagnosis and treatment plans, and monitors progress along the continuum of care. The program encourages dialogue and transparency through tailored reports for both patient and the healthcare provider. The online structure also allows patients and prescribers to effectively interact remotely. Most importantly, PainCAS will be linked with provider and patient educational resources, PainEDU and PainACTION, respectively. Where there is significant concern about utility of voluntary educational resources, given time constraints of clinicians and other factors, PainCAS has the ability to provide education that complements the clinical process, instead of competing with it.

6.6.1.2 PainEDU

With over 50,000 registered users, and 120 ACCME-accredited case-based CE courses for healthcare providers, PainEDU.org is an online, non-promotional, comprehensive pain education resource that offers a variety of educational resources including current relevant pain management information, case studies, opioid risk assessment tools, a library of fully accredited case-based CE courses, and hard-copy materials for reference focused on pain assessment and opioid therapy management. PainEDU provides healthcare provider education for all facets of pain assessment, including use of tools, patient selection, considerations in clinical practice, formulation of treatment plans, and monitoring. It is important to note that participation in PainEDU has been completely voluntary to date. The large participant list, relative to the number of ER/LA opioid prescribers, indicates that meaningful, purposed, and targeted education programs may achieve success in reaching a broad audience.

More importantly, PainEDU also has a variety of print education materials that complements its online components. Many of these materials are utilized through large healthcare systems and medical training programs throughout the country. Finally, PainEDU will provide for virtual patient/mentoring skill-building simulations dealing with difficult pain management cases involving chronic opioid therapy through the NIH-sponsored program Managing Addiction and Pain in Primary Care (MAP-PC) described below.

6.6.1.3 MAP-PC

MAP-PC is an educational program that is being developed with the NIH to assist primary care physicians in acquiring skill sets and knowledge that will help them manage pain patients who may be at increased risk of opioid misuse or abuse. Specifically, the program is designed to support primary care physicians with identification, management, treatment, and pain patient referral, through an engaging virtual standardized patient simulation, and immersive interactive platform. MAP-PC helps physicians make informed decisions about the prescribing opioids while managing the clinical challenges that arise during the course of pain treatment with opioids. While the original development of MAP-PC was limited to primary care physicians in order to pilot the program, MAP-PC is scalable and can be expanded to include other physician sub-group specialties, such as pain specialists across a range of prescriber disciplines. It will include measures that allow for assessments of behavioral change, motivation, and intention to incorporate learnings into clinical practice.

6.6.1.4 PainACTION.com

PainACTION.com is an efficacy-tested, web-based self-management solution designed to educate and empower people with chronic pain. For patients and their caregivers, painACTION provides the resources and knowledge about important topics (e.g., medication safety) through improved communication and education. Registered patients have access to the most up-to-date, tailored information on pain management. PainACTION provides interactive features, tools, and learning modules to help users manage specific types of pain. Published results show that compared to controls, PainACTION pain participants reported significantly lower stress, increased coping skills and greater use of social support. Comparisons between the two groups further showed clinically significant differences in current pain intensity, depression, anxiety, stress and global ratings of improvement (Chiauzzi et al., 2010). This program has a variety of unique, scientifically tested features, and includes an entire curriculum of medication safety courses that are focused on such topics as proper use, storage, and disposal of prescription opioids.

6.6.2 Zogenix Internal Programs

A number of additional safe-use measures will be introduced by Zogenix in addition to the NAVIPPRO intervention and prevention tools described above. These additional programs were selected to compliment both the NAVIPPRO tools and the mandatory safe-use efforts that include DEA scheduling, class-wide labeling and REMS.

6.6.2.1 Prescriber Tool Kit

The Zohydro ER safe use initiative will provide prescribers with a prescriber tool kit. The prescriber kit will provide important components critical to the safe and effective initiation of patients on Zohydro ER, including but not limited to the availability of a new single-entity hydrocodone formulation at different dosage strengths and dosing regimen than current combination hydrocodone products, copies of the medication guide, patient counseling document, information on patient assessment resources, such as eSOAPP and eCOMM, and other information on the keys to effective patient management.

The prescriber kit will be provided to experienced ER/LA opioid prescribers who are targeted by our commercial sales force. The prescriber kit, as well as all of our other safe-use tools, will be available to non-targeted prescribers of Zohydro ER through the Zohydro ER REMS website or the product contact center.

6.6.2.2 Pharmacist Education and Initiatives

Currently, pharmacists are not part of the target group for the recently approved REMS for ER/LA opioid analgesics. In consideration that pharmacists represent the last step in the prescribing and distribution chain before a patient receives a prescription, Zogenix believes it is critical to include this group as yet another resource in the effort to recognize diversion and abuse behaviors in patients. Inflexxion's PainEDU (described in Section 6.6.1.2) will be offered to pharmacists at no cost in order for them to learn more about diversion activities of opioids. Zogenix will also utilize a pharmacy brochure and other communications that will contain information as to how to access this information

6.6.2.3 Patient Treatment Kit

Zogenix will make available to patients a Patient Treatment Kit for patients being newly put on and continuing therapy with Zohydro ER. The kit will contain a copy of the Medication Guide, a reminder of the key points from the Medication Guide, Do's & Don'ts while taking Zohydro ER (excerpted from the patient counseling document), proper disposal tips, and information on how to access pain management resources such as pain advocacy groups and pain education (PainAction, opioids911.org, yourlifesource.org, etc). The Patient Treatment Kit will also contain a voucher enabling the patient to receive, at no cost to them, a safe-keeping product such as a locking cap for the medication bottle or a stand-alone lockbox. This last measure is of key importance, as studies have shown that the vast majority of recreational abusers of prescription opioids obtain their product from family members without their knowledge (Becker 2011). Zogenix believes that emphasizing the safe storage of Zohydro ER, as well as all prescription medications, will mitigate this problem.

6.6.2.4 Opioid Disposal Program

Another mechanism aimed at preventing diversion is to encourage timely disposal of unwanted or unneeded product. Prescription drug abuse is a significant public health and public safety issue, and a large source of the problem is a direct result of what is in Americans' medicine cabinets. SAMHSA's 2010 National Survey on Drug Use and Health found that over 70% of people who used prescription pain relievers non-medically got them

from friends or relatives, while approximately 5% got them from a drug dealer or from the internet. The same survey showed the scale of the problem is vast with more than 7 million Americans reporting use of a prescription medication for non-medical purposes in the past 30 days. Therefore, a plan to address prescription drug abuse must include proper disposal of unused, unneeded, or expired medications. Providing individuals with a secure and convenient way to dispose of medications will help prevent diversion and abuse, and help to reduce the introduction of drugs into the environment.

Zogenix will include information in the Patient Treatment Kits on how to dispose of the product properly, and include both regional and local resources (i.e., telephone numbers or website addresses) for prescription drug take-back programs. Additionally, Zogenix has committed to supporting and sponsoring community-based prescription drug take-back programs to rid patients of unwanted/unneeded prescription drugs that can only be a source of diversion by non-patients.

6.6.3 Pilot Innovative Programs

Beyond the NAVIPPRO programs already described, some of which will be implemented in a pilot effort, Zogenix intends to initiate and test other pilot programs.

In addition to the NAVIPPRO programs, Zogenix will support a urine drug screening program, which is described below.

6.6.3.1 Urine Drug Screening

Much has been written about the utility of urine drug testing in improving care in pain management, but its use remains surprisingly low. In an audit of medical records of 209 adults with chronic pain who had been prescribed opioid analgesics from 74 practitioners in Wisconsin, written treatment agreements were used by 42% of the practitioners, but urinary drug screening was ordered by only 8% (Adams 2001). In a survey of 248 primary care physicians, most expressed concerns about prescription drug abuse (84%) and addiction (75%), but only 7% reported ordering urinary drug screens before prescribing opioids and only 15% reported ordering urinary drug screening as part of ongoing opioid management (Bhamb 2006).

Why is urinary drug screening underutilized in managing patients treated with opioids? One reason may be prescribers treating patients with pain commonly rely on their clinical judgment and intuition when making prescribing decisions, yet these often are inadequate when it comes to identifying patients who might abuse or otherwise misuse their medications (McCarberg 2011). Another reason is that most healthcare providers have little or no training in how best to use urine drug testing or how to interpret results (Pergolizzi 2010).

Urinary drug screening results comprise objective data that support clinical impressions of medication adherence and/or abstinence from substances of abuse. Urinary drug screening serves as an adjunct to a patient's self-report of recent prescription and illicit drug use, since research has established that, for a variety of reasons, patients may not be forthcoming about all medications/drugs they are taking. Additionally, periodic, and preferably random, urinary

drug screening may change behaviors, encouraging patient adherence to prescribed medication regimens and thereby increasing the chances that the therapy will improve pain, function, and quality of life. Finally, in patients who are not experiencing expected pain relief from particular medications, urinary drug screening can suggest pharmacokinetic factors – such as rapid metabolizer phenotypes or CYP450 inducers – that may be responsible for suboptimal analgesia.

As Zohydro ER will be the first single entity hydrocodone marketed, it will be useful and important for prescribers to have information on expected values for urinary levels of hydrocodone and its metabolites in order to provide proper patient management. The company intends to work with a national testing laboratory to develop expected hydrocodone values and metabolite levels.

Additionally, Zogenix believes it can facilitate better patient management if prescribers and patients understand that urinary drug screening will be a routine part of pain management. Routine laboratory testing is usual for a wide range of drug products, and Zogenix is committed to supporting the expectation that routine urine drug screening will be conducted in order to improve patient management by including information in the patient treatment kit.

6.6.4 Surveillance

Zogenix is committed to monitoring the available datasets for evidence of misuse, abuse or accidental overdose. Zogenix supports the use of a number of surveillance systems to monitor the occurrences of intentional and unintentional overdose and abuse of Zohydro ER, as well as diversion activities. As a component of Zogenix' REMS program, NAVIPPRO surveillance will be used to provide an ongoing assessment of Zohydro ER's abuse across various populations in real time. In addition to the NAVIPPRO surveillance tools that Zogenix will use, other surveillance tools include prescription monitoring patterns, cash claims and audit of the supply chain for diversion activities. These are described in detail below.

6.6.4.1 NAVIPPRO Surveillance Programs

As a component of Zogenix' safe-use program, NAVIPPRO surveillance will be used to provide an ongoing assessment of Zohydro ER's abuse across various populations in real time. (

Table 33).

An important question arises for the post-marketing surveillance of any prescription opioid, namely the strategy can be put into place to define and detect an emerging public health problem with respect to abuse and diversion of a new product once it reaches the market. While it is important to monitor population morbidity and mortality associated with any prescription product, including opioids, when a product is first introduced to the market, it is especially important to monitor the proximal indicators of abuse and diversion, indicators that can be measured rapidly and are likely to reflect early warning signs of a particular problem associated with a product. One important reason for selecting NAVIPPRO surveillance tools is that in comparison to the Treatment Episode Data Set (TEDS), which is another commonly used surveillance tool with similar demographic profile, is that the TEDS may have up to a 2 year lag in data timeliness, does not include product specificity, and may not include source of drug. In comparison, the NAVIPPRO surveillance tools provide near real time data, includes product specificity, as well as the source of drug. This makes the NAVIPPRO surveillance tools much more useful in detecting early signs of misuse, abuse and diversion.

Use of NAVIPPRO data to detect an emerging problem with a newly marketed prescription opioid product like Zohydro ER, must take into account the fact that the overall level of abuse is correlated with the prescribed availability of the product (e.g., Butler 2011; Dasgupta 2006). In the early post-marketing phase of Zohydro ER, it would be expected that the prescribed availability of the product is likely to be low, at least initially. During this early stage, monitoring for signals of abuse will focus on:

- All cases of abuse detected in the Addiction Severity Index – Multimedia Version (ASI-MV) and Comprehensive Health Assessment for Teens (CHAT) datasets and to interpret the levels of observed abuse in terms of the product's prescribed availability at the time of observation.
- Route of administration data to monitor the extent to which abusers are employing non-oral routes (e.g., snorting, injection).
- Source data to establish the extent to which the monitored populations of abusers (adults and adolescents) are obtaining the drug through their own prescription from their own doctor, multiple doctors or other sources outside of the normal distribution channels (e.g., friends, family or dealer).

These data would be supported by internet monitoring data that will evaluate the extent to which the recreational abuser population discusses Zohydro ER in terms that suggest high interest and high desirability for the product. Early monitoring available through the Media GRIID data stream provides a metric of diversion through police and media reports of arrests involving Zohydro ER. In combination, the use of the ASI-MV, CHAT and Web Informed Services (WIS) will allow the detection of signals across three very diverse groups, namely, adults, teens, and media sources of information.

Table 33: Description of NAVIPPRO Data Sources to be Included in Surveillance

Addiction Severity Index – Multimedia Version (ASI-MV)	
A self-administered computer-based assessment taken by adults evaluated for substance abuse problems during treatment planning and triage in a network of facilities across the United States.	*Measures:* • Past 30-day abuse of Zohydro ER • Route of administration • Source of drug
Comprehensive Health Assessment for Teens (CHAT)	
A self-administered computer-based assessment taken by adolescents evaluated for substance abuse problems during treatment planning and triage in a network of facilities across the United States.	*Measures:* • Past 30-day abuse of Zohydro ER • Route of administration • Source of drug
Web Informed Services (WIS): Internet Monitoring, Internet Surveys & Media-GRIID	
Internet Monitoring: A proprietary database of online discussion that is systematically collected from selected Internet-based recreational drug use-related website communities.	Internet Monitoring Measures: • Volume of Zohydro ER-related discussion • Opinions, knowledge, experiences, and preferences in relation to prescription opioids as well as Zohydro ER. This includes conversation related to routes of administration, source of drug, and tampering.
Internet Survey: Targeted online surveys of individuals who visit selected Internet-based recreational drug use-related website communities.	Internet Survey Targeted Measures, such as: • Interest in abuse of Zohydro ER • Route of administration • Source of drug • Perceptions
Media GRIID: A proprietary database of systematically collected online news reports that mention prescription-medication-related events.	Media GRIID Measures: • Volume of Zohydro ER-related news media references • News articles related to arrests/abuse, overdose, and pharmacy robbery, among others

6.6.4.2 Zogenix Supply Chain Surveillance

Zogenix will also employ several surveillance tools that monitor the movement of product through the entire supply chain. Zogenix will employ prescription monitoring tools to monitor prescriber volume as well as detect aberrant prescribing patterns. For example, by using IMS data if Zogenix detects prescribers in rural areas writing large numbers of prescriptions that are out of proportion to the population base, Zogenix will investigate and attempt to determine the cause(s) of the prescribing imbalance. Working with the Zohydro ER Safe Use Advisory Board (see below), Zogenix will take the most appropriate response, such as targeted educational offerings. However, if circumstances suggest the potential for illicit behaviors, Zogenix will submit the matter to the proper law enforcement authorities. Similarly, Zogenix will work with supply chain partners and conduct routine audits that include supply chain suspicious ordering groups to detect potential diversion. Pharmacies that exhibit erratic or suspicious ordering patterns will be investigated to determine if shipments of Zohydro ER should be reduced or withheld. For example, erratic or suspicious ordering could manifest itself either by a deviation in baseline ordering (i.e., an increase in the month-to-month ordering) or differences from other opioids ordered by the same pharmacy (eg, comparative analysis). Both of these events represent a signal that would be evaluated by the Safe Use Advisory Board (see below). Finally, Zogenix will monitor prescriptions for the relative proportion of cash to insurance claims as payments for Zohydro ER. Disproportionately high cash payments relative to the other ER/LA opioids are potentially an early indicator of potential diversion. Such disproportionality will be considered a potential signal and evaluated through the Zohydro ER Safe Use Advisory Board.

In cases where Zogenix determines that product may not be properly dispensed and lead to diversion and misuse of the product, Zogenix will always inform law enforcement authorities as well as employ all means possible to terminate supply of the product. Zogenix is committed to stopping completely the supply of product where it is determined that product is not being dispensed properly and is a source of product diversion.

6.6.4.3 Response to Safety Signals

Zogenix recognizes that detection of potential signals of misuse, abuse or unintentional overdose (i.e., safety signals) are only helpful if they result in positive action to mitigate the recognized risk.

Zogenix is committed to using a variety of surveillance tools to monitor the safe use of Zohydro ER. The NAVIPPRO tools were selected as they allow Zogenix to monitor patients, teens and media sources for evidence of abuse, misuse and diversion, thereby enabling a broad cross-section of monitoring. Supplementing those tools are Zogenix supply chain surveillance tools (eg, prescriber prescribing patterns, pharmacy ordering, and cash claims) that enable Zogenix to monitor prescribers, pharmacies and patients for further signs of diversion, and abuse and misuse activities. Through the recommendations of the safe use Advisory Board (see below), Zogenix would use additional surveillance tools if it would provide further meaningful and timely data on abuse, misuse and diversion activities.

Usually, surveillance involves determining if a target condition (in this instance, abuse cases) is increasing over a baseline rate or what would ordinarily be expected. For instance, if influenza is being tracked, the public health question is whether the number of cases this year is greater than would be expected in a normal year. In this way, the outbreak is defined in relation to some baseline occurrence of the disease. When the number of cases is significantly greater than the baseline, a "signal" is detected and reported to public health authorities. Likewise, opioid abuse surveillance assumes that each community has a "baseline" level of abuse (since abuse of abusable substances does occur) and that a signal will entail a significant increase over this level of abuse. A signal could then lead to intervention. Obviously, even the baseline abuse rates of some communities are extremely high. A surveillance system should be able to identify such high risk areas and track ups and downs in this baseline rate as well.

In light of the fact that Zohydro ER will be the first marketed single-entity hydrocodone, there is no baseline by which to compare Zohydro ER events to events associated with another current single-entity hydrocodone. Therefore, in the early stages of product launch a signal could be represented by the first individual report of misuse, abuse, diversion, overdose, or death. Zogenix intends to monitor all such signals to determine if there is a pattern (eg, regional) or if the event frequency seems disproportionate to the prescription volume.

The approach described here is consistent with the evolution of signal detection methods that emphasize integrating quantitative and qualitative analyses of multiple data streams, termed “situation awareness” (e.g., Reis 2007). Situation awareness refers to pulling together available, relevant information from many sources and presenting this information to users/stakeholders in a way that brings meaning to the data and allows coherent responses to actionable events (e.g., DeFraites & Chambers, 2007). This approach represents a shift away from establishing a more-or-less arbitrary numerical threshold (e.g., $\geq$ 5 cases/100,000 population; Cicero 2005). Situation awareness encourages the use of near real-time data in a way that makes possible rational and timely responses to the data (e.g., Brownstein 2009; Chretien 2008).

After launch and when the product prescription volume has increased, it will be more appropriate to evaluate signals either based on comparison to other ER/LA opioid products (eg, relative abuse rates), or deviation from a baseline. Subsequent activities will include increased communications to the stakeholder group involved (eg, patients, teens, etc) to inform as to the differences from lower dose hydrocodone combination products and the risks of overdose.

Signals that suggest Zohydro ER may be distributed to problematic pharmacies will be addressed by working with supply chain partners and integrating with their Suspicious Order Monitoring Programs. When signals point to potential violations of regulations or laws, Zogenix intends to inform relevant law enforcement or regulatory agencies.

All potential safety signals will be evaluated by trained Zogenix employees working under explicit Standard Operating Procedures requiring escalation of confirmed or indeterminate safety signals to the senior management of the company. Working in concert with the Safe

Use Advisory Board (outlined below) Zogenix's senior management will be responsible for confirming, rejecting or referring for additional evaluation all potential safety signals. Once a safety signal has been confirmed, various responses to that signal are available, including focusing educational outreach to the at-risk population or the healthcare professionals that serve that population. The targeted education can take the form of additional professional continuing education opportunities, educational outreach directly to patients regarding safe storage and handling information, or interactions with law enforcement regarding proper drug disposal opportunities within a geographic region. Additional response options include restricting the distribution of Zohydro ER within a geography, pursuing changes to Zohydro ER's prescribing information, initiating additional safety activities, sharing observations with public health officials or law enforcement agencies or withdrawal of commercial sales activity to that geography. Above all else, the senior management of Zogenix, from the CEO on down, recognize and accept their shared responsibility to be good stewards of this product.

6.6.4.4 External Advice and Oversight

An independent Safe Use Advisory Board will be established to assist the company in interpreting the results of the various surveillance activities. The Safe Use Advisory Board will receive the data streams from the Inflexxion surveillance tools (which includes cases of abuse reported through the ASI-MV, CHAT and police and media reports), prescriber and pharmacy prescribing patterns, prescription cash claims and adverse events of interest. The Board exists to guide and oversee Zogenix' evaluation of these data streams for potential signals indicating diversion, abuse and misuse. Additionally, the Advisory Board will help to shape Zogenix' efforts to confirm potential safety signals and devise appropriate responses once a signal is confirmed.

This Advisory Board will provide Zogenix senior management (CEO, President, Vice President Regulatory Affairs & Drug Safety, Compliance Officer) a summary of their interpretation of the available data and make recommendations to Zogenix regarding how best to understand the available data, any actions to be taken to further minimize product risk, assist with publication of safe-use data, and identify areas for program improvement. To ensure the timely escalation of critical safety information, the Safe Use Advisory Board will have direct access to the Zogenix Board of Directors and will be authorized to report the results of their deliberations directly to the FDA if they choose to do so.

Zohydro ER Safe Use Advisory Board	
Practicing Pain Management Clinician	Pharmacovigilance Expert
Practicing Addiction Management Clinician	Epidemiology or Risk Management Expert
Surveillance Expert	

6.7 Summary – Zohydro ER Safe Use Initiative

Zogenix intends to undertake a multimodal and multi-axial program designed to maximize the safe use of Zohydro ER. The cornerstone and underpinning of this program is the

commitment to aggressively execute the requirements of the Zohydro ER REMS. These activities are supplemented by additional steps undertaken by Zogenix. The combination of these two risk mitigation efforts culminates in the Zohydro ER risk management cascade. Designed in a continuous improvement loop, the cascade starts with the generation of potential safety signals that undergo review and amplification by Zogenix professionals. The Zohydro ER Safe Use Advisory Committee is used as a signal confirmation step and a source of guidance for appropriate risk mitigation activities. The chosen safety responses will be tracked for effectiveness and the learnings from each episode will be fed back into the signal generation and signal review steps of the process. It is through repetitions of the signal, signal response and evaluation cycle that the overall risk mitigation of Zohydro ER will be enhanced.

The unfortunate reality of the prescription medicine abuse epidemic that faces our nation is that it is difficult to offer beneficial opioid therapy to patients suffering from chronic pain without also incurring the cost of individual harm stemming from misuse and abuse of the product. Individual misuse and abuse of prescription medication cannot be entirely corrected by the actions of a single manufacturer, or even a coalition of manufacturers working in concert with state, local, and federal government agencies. However, Zogenix believes that Zohydro ER can benefit patients suffering with chronic pain. Through our proposed and novel safe use initiatives and selective commercialization strategies, coupled with a commitment to overall responsible marketing, we can contribute to a positive trend of appropriate and safe use of opioids for the appropriate patients.

7 BENEFIT-RISK SUMMARY

7.1 Intended Use

It is important to place the benefit-risk assessment into the appropriate context in which the new product will be used. While hydrocodone is a very widely prescribed medication (primarily in the form of combination products containing acetaminophen), only about 5% of patients currently prescribed hydrocodone progress to chronic use at sufficient doses that would merit consideration of an extended-release product. When they meet clinical criteria for the addition of an extended-release product; they are typically patients with around-the-clock moderate to severe pain, who have significant pain interference with sleep, awaken with pain, may have peak-dose side effects, and may need to take medication every few hours. Physicians are generally trained to use the same molecule when adding an extended-release opioid to an immediate-release regimen, in order to take advantage of the idiosyncratic efficacy and tolerability often seen with opioids. In such patients on immediate-release hydrocodone, there has been no extended-release option, necessitating using extended-release formulations of other molecules.

The subjects who volunteered to participate in the Zohydro Phase 3 studies represented a group with severe chronic pain which was not being adequately controlled and needed alternative treatment. More than half of them had an initial pain score greater than 7 out of 10, and in Study 801 more than half had an Oswestry Disability Index above 60 out of 100, with 93% categorized at study entry as having severe disability, being crippled, or bedridden.

Patient populations of this type are common in chronic pain and, as the clinical data demonstrate, would benefit from this treatment option.

Zohydro ER represents an incremental but significant addition to available therapies. It fills a modest but important gap and will be particularly useful for treating patients with chronic pain who are currently doing well on treatment that includes immediate-release hydrocodone, but have developed the need for continuous, around the clock opioid therapy. They would benefit from having hydrocodone available as their first extended release opioid. Another population that would benefit from this medication is patients with chronic pain who are taking an extended release opioid in a continuous, around the clock regimen, but who require a different extended release opioid because they are or become intolerant to the current one, or because of a loss of effectiveness.
There are people with chronic pain who would benefit from treatment with hydrocodone but who cannot take it in any of its current combination forms, either because of gastric, renal or bleeding issues (HC/ibuprofen), or more particularly because of hepatic sensitivity (HC/APAP). A considerable proportion of people with chronic pain should be treated cautiously if at all with acetaminophen. This includes those with hepatic impairment or active liver disease, alcoholism, chronic malnutrition, hypovolemia, severe renal impairment or in those allergic to acetaminophen. Taking acetaminophen in doses above the recommended maximum of 4000 mg per day may result in hepatic injury, including the risk of severe hepatotoxicity and death. People with chronic pain who achieve satisfactory pain relief with acceptable side effects using HC/APAP may be tempted to take higher doses when they develop tolerance, leading them to exceed the recommended maximum daily dose of acetaminophen. Others may exceed the safe limits of APAP usage by combining HC/APAP with OTC products containing APAP. Zohydro ER would represent an important alternative in either case.

7.2 Benefits of Zohydro ER (HC-ER)

How does one measure benefit in a chronic pain program? The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) published a set of core domains that should be considered for inclusion in clinical trials of chronic pain treatment efficacy and effectiveness based on a consensus meeting of specialists from academia, governmental agencies including the FDA, and the pharmaceutical industry (Turk 2003). The Zohydro ER studies generated positive results in each domain (Pain, Physical functioning, Emotional functioning, and Participant ratings of Global Improvement).

The efficacy of Zohydro ER compared to placebo was robust across a variety of standard methods for examining pain intensity in clinical trials. Zohydro ER was superior to placebo in relieving pain on group mean difference in pain intensity (average daily pain intensity scores—the primary study endpoint, $p = 0.008$), and on measures of clinically meaningful individual improvement in pain intensity (30% response rate ($p<0.001$) and 50% response rate ($p<0.001$), which are considered “clinically important” and “major” improvement, respectively). In addition, subjects on Zohydro ER had a significantly longer time-to-exit due to loss of efficacy compared to placebo ($p < 0.001$), which is an important and statistically powerful measure of analgesic efficacy. It should be noted that the enriched

enrollment randomized withdrawal study design is in some ways more relevant to clinical practice than standard parallel treatment designs, as patients are titrated in an open-label phase on active treatment, as is done in clinical practice. In this phase, mean pain score was reduced from 7 to 3 (0-10 numerical rating scale), a substantial improvement in pain intensity that was sustained for more than half the patients, many of whom would have been candidates for more aggressive interventional pain treatments if pharmacotherapy had failed. On a measure of physical functioning (the ODI), mean ODI scores were reduced from Screening to the end of study, and were significantly lower for the Zohydro ER group (53.2 ± 13.9) compared to the placebo group (57.6 ± 16.6, p=0.026). Four points has been suggested as the minimum difference in mean scores between groups to constitute clinical significance (Meade 1995). To inform how these group differences translate into individual improvement, it is sometimes useful to perform item-level analysis. As noted above, these subjects suffered a high level of functional impairment at screening. The proportion of subjects with minimal disability was decreased during treatment, and the number of subjects who reported they were crippled or bedridden decreased. These results are reassuring not only because of the improvements in physical function they represent, but also because any side effects of the treatment do not override their benefits in this domain.

Chronic pain is often associated with emotional distress, particularly depression, anxiety, anger, and irritability and improvements in this domain are central in people's assessments of their well-being and satisfaction with life (Turk 2003). In the emotional domain, patients on Zohydro ER showed no negative impact on anxiety and depression, which are typically measured in clinical studies of opioid analgesics to ensure that there is no deterioration of mood while on therapy, and to potentially detect any benefit. As shown by the Hospital Anxiety and Depression Scale, a validated and commonly used measure of mood in clinical trials, Zohydro ER compared with placebo actually produced an improvement in depression during the maintenance treatment phase of Study 801 ($p = 0.006$).

Global evaluations by participants in clinical trials of the benefits of treatment reflect not only the magnitude of the changes in pain and function, but also the personal importance that these outcomes have for participants (Turk 2003). Patient global rating in the Zohydro ER trial was performed using the Subject Global Assessment of Medication (SGAM). The mean change from screening to Day 85 in SGAM score was 0.8 units for the Zohydro ER group, compared with 0.0 units for the placebo group. This difference between treatment groups was statistically significant ($p<0.001$), indicating a greater degree of satisfaction with Zohydro ER than with placebo, and 0.8 is a clinically meaningful change for this 5-point scale. As expected, only a very small proportion of subjects (13-19%) were very much or completely satisfied with their pain medication when they entered the study, prior to receiving Zohydro ER. At the time of randomization, after open-label treatment with Zohydro ER in the conversion/titration phase of the study, 73-77% were very much or completely satisfied with their pain medications. Over the course of the 12-week blinded maintenance phase, the proportion of the subjects very much or completely satisfied with their pain medications in the group randomized to receive Zohydro ER remained high at 64%, with a lower proportion similarly satisfied in the placebo group at 35%.

Acetaminophen can lead to liver damage and acute liver failure when used excessively. Data presented at an FDA advisory committee in 2009 and reviewed recently (Mincha 2010)

showed that APAP overdose was the leading cause of acute liver failure in the US, and that 63% of the unintentional overdoses were associated with ingestion of opioid/APAP combination products. The FDA Advisory Committee voted (20-17) to recommend removal of opioid/APAP combinations from the market. However, it was noted at the meeting that, without a single agent hydrocodone available, elimination of these medications could have deleterious consequences on the practice of pain management. It seems likely that some excessive APAP dosing is driven by pain patients' need for larger doses of hydrocodone once tolerance develops. Since hydrocodone is not available as a single agent, patients self-treat their pain by taking ever higher and excessive doses of HC/APAP. HC/APAP is a suboptimal treatment for patients with chronic pain, because only low doses hydrocodone forms are available (up to 10 mg) with fixed doses of APAP (currently up to 750 mg, eventually to be limited to 325 mg). However, HC/APAP is commonly prescribed and commonly used for treatment of chronic pain, due in part to patients' and prescribers' familiarity and comfort with hydrocodone. A key benefit of making Zohydro ER available will be to allow escalation of hydrocodone doses in patients with chronic pain patients with no concomitant acetaminophen burden. Another benefit is that substantial numbers of people with chronic pain cannot take acetaminophen because of existing liver dysfunction or conditions that enhance the hepatotoxic effects of acetaminophen such as alcoholism, dehydration, and use of certain concomitant medications. For these patients, hydrocodone would be available for the first time to treat their chronic moderate to severe pain.

7.3 Risks of Zohydro ER (HC-ER) and Risk Mitigations

While risks of opioid analgesics are well known, it is important to review the risk profile of Zohydro ER compared to other extended release opioids to ensure there is no new or unexpected safety signal. The most common TEAEs, occurring in greater than 5% of the integrated study subjects, were constipation (15.4%), nausea (13.4%), headache (8.3%), somnolence (7.8%), vomiting (7.1%), back pain (5.7%), and fatigue (5.1%). Typical opioid adverse events did not appear to occur at a substantially greater frequency with Zohydro ER at hydrocodone doses above 100 mg per day. No new or unexpected adverse events were discovered in this analysis, which shows that Zohydro ER treatment is associated with the type and frequency of adverse events that are typical of opioids and extended release opioids in particular. This risk will be managed by including a comprehensive adverse event profile in the Zohydro ER Prescribing Information. These messages will be repeated, expanded and emphasized, and side effect prevention and management strategies will be included in promotional materials and in materials provided through the Zohydro ER Safe Use Initiative programs.

Overdose is a serious risk of any immediate-release or sustained release opioid analgesic. There was no signal of any enhanced overdose risk from the Zohydro ER clinical program compared to other marketed opioids. Like many other extended-release opioid analgesics, Zohydro ER can be crushed or dissolved to release the active moiety from the slow release matrix, and the resultant amounts of free hydrocodone could cause overdose if ingested in excessive amounts. The Zohydro ER Prescribing Information will state, "The capsules must be swallowed whole and must not be chewed, crushed, or dissolved. Taking chewed, crushed

or dissolved Zohydro ER capsules or contents can lead to rapid release and absorption of a potentially fatal dose of hydrocodone" in several places, and "Tampering with or altering the capsule can result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death". These messages will be repeated, expanded and emphasized in promotional materials and in materials provided through the ER/LA Opioid REMS and Zohydro Safe Use Initiative programs. Like many other extended-release opioid analgesics, initial Zohydro ER blood levels can be increased by co-ingestion with high amounts of alcohol. The Zohydro ER Prescribing Information will state, "The co-ingestion of alcohol with Zohydro ER may result in increased plasma levels and a potentially fatal overdose of hydrocodone. Patients must not consume alcoholic beverages, or prescription or non-prescription medications containing alcohol, while on Zohydro ER therapy" in several places, and contains a Warning of, "Additive CNS-depressive effects when used in conjunction with alcohol, other opioids, or illicit drugs", and will state, "Consider the patient's use, if any, of alcohol and/or illicit drugs that cause CNS depression. If the decision to begin Zohydro ER is made, start with a lower Zohydro ER dose than usual". These messages will be repeated, expanded and emphasized in promotional materials and in materials provided through the ER/LA Opioid REMS and Zohydro ER Safe Use Initiative programs.

Reducing serious outcomes such as addiction, unintentional overdose and death from inappropriate prescribing, diversion, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access is a major legal, regulatory, industry and societal issue. Zogenix recognizes that its new formulation of extended release hydrocodone has significant abuse potential, equal to other ER/LA opioid analgesics, and is committed to commercializing the product in a manner that mitigates that liability. Measures that are expected to reduce risk include a Schedule II prescribing status, and the FDA's new ER/LA opioid REMS program. However, Zogenix is committed to undertaking a substantial number of additional risk mitigating activities under its Zohydro ER Safe Use Initiative program, which was described and discussed extensively in this Briefing Document. Several of the unique programs will be evaluated extensively through regional effectiveness assessments, and the results of the research will be shared publically to improve risk mitigation efforts for both public agencies and the industry.

7.4 Benefit-Risk Summary

Taken together, the benefits of making Zohydro ER available to patients with chronic pain outweigh the risks. The clinical benefits include pain relief, reduction in disability and increased patient satisfaction with pain medication. Other benefits include the availability of hydrocodone in extended release form when chronic pain patients are first converted from a regimen of immediate release HC/APAP, and the addition of Zohydro ER to prescribers' choices when there is a need to change from one extended-release opioid to another for reasons of tolerability or falling efficacy. The risks include opioid adverse events, accidental overdose with therapeutic usage, unintentional overdose and death from inappropriate prescribing, addiction, diversion, misuse, and abuse. Measures that are expected to reduce risk include a Schedule II prescribing status, the FDA's new ER/LA opioid REMS program, and the Zohydro ER Safe Use Initiative program.

The rigorous and vigilant oversight and compliance program that was undertaken and executed during the registration clinical program is representative of the company's attitudes and planned philosophy for marketing Zohydro ER. Zogenix believes that there is a strong medical need for this product, but that it must be introduced into clinical usage with appropriate safeguards and oversight. The company's experiences and policies during the clinical trials represent an excellent framework of responsible prescribing, vigorous training and education, and vigilant oversight with immediate and aggressive corrective actions that foreshadows the Zogenix approach to commercializing Zohydro ER in the most responsible manner possible.

In conclusion, the data presented in this Briefing Document demonstrate that Zohydro ER is effective in relieving moderate to severe chronic pain. The safety profile of Zohydro ER was consistent from the two largest studies, and was consistent with the safety profiles of other opioid medications with no new or unexpected toxicities observed. Zogenix is committed to a conservative commercialization strategy while making real progress in understanding the value of different approaches to mitigating risks. Overall the benefits of Zohydro ER for patients exceed the risks associated with this new formulation, in the context of a responsible Zohydro ER commercialization plan.

8 LITERATURE CITED

<*Available upon request.*>

Adams EH, Breiner S, Cicero TJ, Geller A, Inciardi JA, Schnoll SH, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage. 2006 May;31(5):465-76.

Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA, Stauffacher EA. Opioids and the treatment of chronic pain in a primary care sample. Journal of Pain and Symptom Management. 2001;22(3):791-6.

Arnow BA, Hunkeler EM, Blasey CM, Lee J, Constantino MJ, Fireman B, et al. Comorbid depression, chronic pain, and disability in primary care. Psychosom Med. 2006 Mar-Apr;68(2):262-8.

Becker WC, Tobin DG, Fiellin DA. Nonmedical use of opioid analgesics obtained directly from physicians: Prevalence and correlates. Archives of Internal Medicine. 2011;171(11):1034-6.

Bhamb B, Brown D, Hariharan J, Anderson J, Balousek S, Fleming MF. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. Current Medical Research and Opinion. 2006;22(9):1859-65.

Bromberg J, Wood, M. E., Black, A., Surette, D. A., Zacharoff, K. L., & Chiauzzi, E.A randomized trial of web-based intervention to improve migraine self-management and coping. Headache. 2012;52(2):244-261.

Brownstein JS, Freifeld CC, Madoff LC. Digital disease detection: Harnessing the Web for public health surveillance. New England Journal of Medicine. 2009;360:2153-2157.

Burch F, Fishman R, Messina N, Corser B, Radulescu F, Sarbu A, et al. A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. Pain Symptom Manage. 2007 Sep;34(3):328-38.

Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. Harm Reduct J. 2011;8:29.

Butler SF, Budman SH, Fanciullo GJ, Jamison RN. Cross validation of the current opioid misuse measure to monitor chronic pain patients on opioid therapy. Clinical Journal of Pain. 2010;26(9):770-776.

Butler SF, Budman SH, Fernandez KC, Fanciullo GJ, Jamison RN. Cross validation of a screener to predict opioid misuse in chronic pain patients (SOAPP-R). Journal of Addiction Medicine. 2009;3(2):66-73.

Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the revised screener and opioid assessment for patients with pain (SOAPP-R) J Pain. 2008;9:360-72.

Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain. 2004;112:65-75.

Caldwell JR, Hale ME, Boyd RE, Hague JM, Iwan T, Shi M, Lacouture PG. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol. 1999 Apr;26(4):862-9.

CDC.gov [internet]. Georgia. Available from http://www.cdc.gov/.

Chiauzzi E, Pujol, LA, Wood, M., Bond, K., Black, R., Yiu, E., & Zacharoff, K. painACTION-back pain: A self-management website for people with chronic back pain. Pain Medicine. 2010;11(7):1044-1058.

Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain. 2009 Feb;10(2):113-30.

Chretien JP, Burkom HS, Sedyaningsih ER, Larasati RP, Lescano AG, Mundaca CC, et al. Syndromic surveillance: adapting innovations to developing settings. PLoS Med. 2008 Mar 25;5(3):e72.

Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002-2004. J Pain. 2005;6(10):662-72.

Dasgupta N, Kramer ED, Zalman MA, Carino S, Smith MY, Haddox JD, and Wright CT: Association between non-medical and prescriptive usage of opioids. Drug and Alcohol Dependence. 2006;82:135-142.

DeFraites RF, Chambers WC. Gaining experience with military medical situational awareness and geographic information systems in a simulated influenza epidemic. Military Medicine. 2007;172:1071-1076.

Dersh J, Gatchel RJ, Polatin P, Mayer T. Prevalence of psychiatric disorders in patients with chronic work-related musculoskeletal pain disability. J Occup Environ Med. 2002 May;44(5):459-68.

Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al.; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005Jan;113(1-2):9-19.

Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. JAMA. 2005 Jun 22;293(24):3043-52.

Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. Pain Med. 2003 Dec;4(4):331-9.

Embeda (package insert). Bristol, TN: King Pharmaceuticals, Inc.; Jul 2012.

Fairbank JC, Pynsent PB. The Oswestry Disability Index. Spine. 2000;25(22):2940-2952.

Fishman SM, Gilson AM. Commentary to Michna et al.: The elephant in the room: hydrocodone/acetaminophen combination compounds and the substitution effect. Pain Medicine. 2010;11(3):379-81.

Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, et al. The rising prevalence of chronic low back pain. Arch Intern Med. 2009 Feb 9;169(3):251-8.

Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. J Opioid Manag. 2011 May-Jun;7(3):193-202.

Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ. 2006 May 23;174(11):1589-94.

Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone ER in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. J Pain. 2005 Jan;6(1):21-8.

Hale ME, Ahdieh H, Ma T, Rauck R; Oxymorphone ER Study Group 1. Efficacy and safety of OPANA ER (oxymorphone ER) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. J Pain. 2007 Feb;8(2):175-84.

Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin. 2010 Jun;26(6):1505-18.

Harkness EF, Macfarlane GJ, Silman AJ, McBeth J. Is musculoskeletal pain more common now than 40 years ago?: Two population-based cross-sectional studies. Rheumatology (Oxford). 2005 Jul;44(7):890-5.

Ho T, Vrabec JT, Burton AW. Hydrocodone use and sensorineural hearing loss. Pain Physician. 2007 May;10(3):467-72.

Hutchinson MR, Menelaou A, Foster DJ, Coller JK, Somogyi AA. CYP2D6 and CYP3A4 involvement in the primary oxidative metabolism of hydrocodone by human liver microsomes. Br J Clin Pharmacol. 2004 Mar;57(3):287-97.

http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM163652.pdf (accessed 02Sep2012).

http://www.fda.gov/AdvisoryCommittees/Calendar/ucm143083.htm

http://www.samhsa.gov/data/nsduh/2k10nsduh/2k10results.htm

Institute of Medicine (IOM). Relieving pain in America: a blueprint for transforming prevention, care, education, and research. The National Academies Press, Washington, DC. 2011.

Ishiyama A, Ishiyama G, Baloh RW, Evans CJ. Heroin-induced reversible profound deafness and vestibular dysfunction. Addiction. 2001Sep;96(9):1363-4.

Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. Spine (Phila Pa 1976). 1998 Dec 1;23(23):2591-600.

Johnson F, Wagner G, Sun S. Effect of Concomitant Ingestion of Alcohol on the In Vivo Pharmacokinetics of KADIAN (Morphine Sulfate Extended-Release) Capsules. J Pain. 2008 Apr;9(4):330-6.

Kaplan HL, Busto UE, Baylon GJ, Cheung SW, Otton SV, Somer G, et al. Inhibition of cytochrome P450 2D6 metabolism of hydrocodone to hydromorphone does not importantly affect abuse liability. J Pharmacol Exp Ther. 1997Apr;281(1):103-8.

Katz N. Opioids: after thousands of years, still getting to know you. Clin J Pain. 2007 May;23(4):303-6.

Katz N, Hale M, Morris D, Stauffer J. Morphine sulfate and naltrexone hydrochloride ER capsules in patients with chronic osteoarthritis pain. Postgrad Med. 2010Jul;122(4):112-28.

Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R, Podolsky G. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone ER for opioid-naive patients with chronic low back pain. Curr Med Res Opin. 2007 Jan;23(1):117-28.

Manchikanti L, Helm S, 2nd, Fellows B, Janata JW, Pampati V, Grider JS, et al. Opioid epidemic in the United States. Pain Physician. 2012 Jul;15(3 Suppl):ES9-38.

Manchikanti L, Abdi S, Atluri S, Balog CC, Benyamin RM, Boswell MV, et al. American Society of Interventional Pain Physicians (ASIPP) guidelines for responsible opioid prescribing in chronic non-cancer pain: Part I - Evidence Assessment. Pain Physician. 2012b Jul;15(3 Suppl):S1-S66.

McCarberg BH. A critical assessment of opioid treatment adherence using urine drug testing in chronic pain management. Postgraduate medicine. 2011;123(6):124-31.

Meade TW, Dyer S, Browne W, et al. Randomized comparison of chiropractic and hospital outpatient management for low-back-pain - results from extended follow-up. BMJ. 1995;311:349–51.

Merskey H, Bugduk N. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms, 2nd ed. Seattle, WA, IASP Press; 1994.

Michna E, Duh MS, Korves C, Dahl JL. Removal of opioid/acetaminophen combination prescription pain medications: assessing the evidence for hepatotoxicity and consequences of removal of these medications. Pain Medicine. 2010;11(3):369-78.

National Institute of Neurological Disorders and Stroke, National Institute of Health Chronic Pain Information Page.

Nalamachu S, Hassman D, Wallace MS, Dumble S, Derrick R, Howell J. Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain. Current Medical Research and Opinion. 2011;27(3):519-30.

Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010(1):CD006605.

Nucynta® ER (package insert). Titusville, NJ: Janssen Pharmaceuticals, Inc.; Jul 2012.

Opana® ER (package insert). Chadds Ford, PA: Endo Pharmaceruticals, Inc.; Jul 2012

Otton SV, Schadel M, Cheung SW, Kaplan HL, Busto UE, Sellers EM. CYP2D6 phenotype determines the metabolic conversion of hydrocodone to hydromorphone. Clin Pharmacol Ther. 1993 Nov;54(5):463-72.

Papaleontiou M, Henderson CR, Jr., Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2010 Jul;58(7):1353-69.

Parsells Kelly J, Cook SF, Kaufman DW, Anderson T, Rosenberg L, Mitchell AA. Prevalence and characteristics of opioid use in the US adult population. Pain. 2008;138(3):507-13.

Pasternak GW. Insights into mu opioid pharmacology: The role of mu opioid receptor subtypes. Life Sciences. 2001;68(19-20):2213-9.

Pergolizzi J, Pappagallo M, Stauffer J, Gharibo C, Fortner N, De Jesus MN, et al. The role of urine drug testing for patients on opioid therapy. Pain Practice. 2010;10(6):497-507.

Portenoy RK, Farrar JT, Backonja M-M, Cleeland CS, Yang K, Friedman M, et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. The Clinical Journal of Pain. 2007;23(4):287-99.

Reis BY, Kirby C, Hadden LE, Olson K, Mcmurry AJ, Daniel JB, Mandl KD. AEGIS: A robust and scalable real-time public health surveillance system. Journal of the American Medical Informatics Association. 2007;14:581–588.

Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, Rauschkolb C. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011 Jan;27(1):151-62.

Slatkin NE. Opioid switching and rotation in primary care: implementation and clinical utility. Curr Med Res Opin. 2009 Sep;25(9):2133-50.

Source Healthcare Analytics, Source ® PHAST Prescription Monthly, September 2011 – August 2012.

Steiner DJ, Sitar S, Wen W, Sawyer G, Munera C, Ripa SR, Landau C. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naïve patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage. 2011 Dec;42(6):903-17.

Stoops WW, Hatton KW, Lofwall MR, Nuzzo PA, Walsh SL. Intravenous oxycodone, hydrocodone, and morphine in recreational opioid users: abuse potential and relative potencies. Psychopharmacology (Berl). 2010 Oct;212(2):193-203.

Temple, 2012: www.fda.gov/Drugs/NewsEvents/ucm295054.htm - 12k - 2012-06-20 - Cached.

Turk DC, Dworkin RH, Allen RR, Bellamy N, Brandenburg N, Carr DB, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain. 2003 Dec;106(3):337-45.

Von Korff M, Crane P, Lane M, et al. Chronic spinal pain and physical-mental comorbidity in the United States: results from the national comorbidity survey replication. Pain. 2005;113(3):331-339.

Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, Ruckes C, Weber S, Grothe B, Fleischer W, Reimer K. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain. 2008;9:1144–54.

Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. J Opioid Manag. 2008 Mar-Apr;4(2):87-97.

Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR, Jr. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend. 2008 Dec 1;98(3):191-202.

Wild JE, Grond S, Kuperwasser B, Gilbert J, McCann B, Lange B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Practice. 2010;10(5):416-27.

Wightman R, Perrone J, Portelli I, Nelson L. Likeability and abuse liability of commonly prescribed opioids. Journal of Medical Toxicology. 2012:1-6.

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatrica Scandinavica. 1983;67(6):361-70.

9 APPENDICES

9.1 Appendix 1 Disability and Satisfaction Scales

9.2 Appendix 2 Meta Analysis of EERW Pain Studies

9.3 Appendix 3 Zohydro ER Medication Guide

9.4 Appendix 4 Zohydro ER Patient Counseling Document

9.5 Appendix 5 FDA ER/LA Opioid REMS

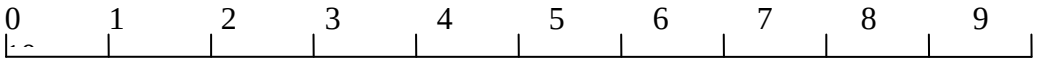
Advisory Committee Briefing Materials: Available for Public Release

Appendix 1 – STUDY ZX002-0801 SUBJECT REPORTED OUTCOME SCALES

0-10 NRS pain intensity measurement

Pain intensity over the past 24 hours was recorded daily (i.e., at bedtime) by the subject in an electronic diary using the 0-10 NRS.

The 0-10 scale below was used to measure the intensity of pain, with 0 being no pain and 10 being the most intense pain. Subjects indicated the number from 0 to 10 that corresponded to the intensity of their average pain in the past 24 hours, their least pain in the last 24 hours, and their worst pain in the past 24 hours.



subject global assessment of medication

Subject Global Assessment of Medication was performed at Screening (assessment of pre-study opioid medication), Baseline and Day 85 (assessment of HC-ER). These assessments were completed in the clinic and recorded electronically by the subject. The following question was asked:

How satisfied are you with your pain medication? (Completed by the subject)

- ☐ Not at all
- ☐ A little bit
- ☐ Moderately
- ☐ Very much
- ☐ Completely

Scoring:

Not at all = 0 point
A little bit = 1 point
Moderately = 2 points
Very much = 3 points
Completely = 4 points

Oswestry disability index (ODI)

The ODI was assessed at Screening, Baseline, and Day 85. These assessments were completed in the clinic and recorded electronically by the subject.

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking **one box in each section** for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement **which most clearly describes your problem.**

Section 1: Pain Intensity

- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2: Personal Care (eg. washing, dressing)

- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but can manage most of my personal care
- ☐ I need help every day in most aspects of self-care
- ☐ I do not get dressed, wash with difficulty and stay in bed

Section 3: Lifting

- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives me extra pain
- ☐ Pain prevents me lifting heavy weights off the floor but I can manage if they are conveniently placed eg. on a table
- ☐ Pain prevents me lifting heavy weights but I can manage light to medium weights if they are conveniently positioned
- ☐ I can only lift very light weights
- ☐ I cannot lift or carry anything

Section 4: Walking*

- ☐ Pain does not prevent me walking any distance
- ☐ Pain prevents me from walking more than 2 kilometres
- ☐ Pain prevents me from walking more than 1 kilometre
- ☐ Pain prevents me from walking more than 500 metres
- ☐ I can only walk using a stick or crutches
- ☐ I am in bed most of the time

Section 5: Sitting

- ☐ I can sit in any chair as long as I like
- ☐ I can only sit in my favourite chair as long as I like
- ☐ Pain prevents me sitting more than one hour
- ☐ Pain prevents me from sitting more than 30 minutes
- ☐ Pain prevents me from sitting more than 10 minutes
- ☐ Pain prevents me from sitting at all

Section 6: Standing

- ☐ I can stand as long as I want without extra pain
- ☐ I can stand as long as I want but it gives me extra pain
- ☐ Pain prevents me from standing for more than 1 hour
- ☐ Pain prevents me from standing for more than 30 minutes
- ☐ Pain prevents me from standing for more than 10 minutes
- ☐ Pain prevents me from standing at all

Section 7: Sleeping

- ☐ My sleep is never disturbed by pain
- ☐ My sleep is occasionally disturbed by pain
- ☐ Because of pain I have less than 6 hours sleep
- ☐ Because of pain I have less than 4 hours sleep
- ☐ Because of pain I have less than 2 hours sleep
- ☐ Pain prevents me from sleeping at all

Section 8: Sex Life (if applicable)

- ☐ My sex life is normal and causes no extra pain
- ☐ My sex life is normal but causes some extra pain
- ☐ My sex life is nearly normal but is very painful
- ☐ My sex life is severely restricted by pain
- ☐ My sex life is nearly absent because of pain
- ☐ Pain prevents any sex life at all

Section 9: Social Life

- ☐ My social life is normal and gives me no extra pain
- ☐ My social life is normal but increases the degree of pain
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests e.g. sport
- ☐ Pain has restricted my social life and I do not go out as often
- ☐ Pain has restricted my social life to my home
- ☐ I have no social life because of pain

Section 10: Travelling

- ☐ I can travel anywhere without pain
- ☐ I can travel anywhere but it gives me extra pain
- ☐ Pain is bad but I manage journeys over two hours
- ☐ Pain restricts me to journeys of less than one hour
- ☐ Pain restricts me to short necessary journeys under 30 minutes
- ☐ Pain prevents me from travelling except to receive treatment

Score: / **x 100 =** **%**

Scoring: For each section the total possible score is 5: if the first statement is marked the section score = 0, if the last statement is marked it = 5. If all ten sections are completed the score is calculated as follows:

Example: 16 (total scored)
50 (total possible score) x 100 = 32%

If one section is missed or not applicable the score is calculated: 16 (total scored)
45 (total possible score) x 100 = 35.5%

Minimum Detectable Change (90% confidence): 10%points (Change of less than this may be attributable to error in the measurement)

Source: Fairbank JCT & Pynsent, PB (2000) The Oswestry Disability Index. *Spine*, 25(22):2940-2953.
Davidson M & Keating J (2001) A comparison of five low back disability questionnaires: reliability and responsiveness. Physical Therapy 2002;82:8-24.

*Note: Distances of 1mile, ½ mile and 100 yards have been replaced by metric distances in the Walking section.

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking **one box in each section** for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement **which most clearly describes your problem.**

Section 1: Pain Intensity

- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2: Personal Care (eg. washing, dressing)

- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but can manage most of my personal care
- ☐ I need help every day in most aspects of self-care
- ☐ I do not get dressed, wash with difficulty and stay in bed

Section 3: Lifting

- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives me extra pain
- ☐ Pain prevents me lifting heavy weights off the floor but I can manage if they are conveniently placed eg. on a table
- ☐ Pain prevents me lifting heavy weights but I can manage light to medium weights if they are conveniently positioned
- ☐ I can only lift very light weights
- ☐ I cannot lift or carry anything

Section 4: Walking*

- ☐ Pain does not prevent me walking any distance
- ☐ Pain prevents me from walking more than 2 kilometres
- ☐ Pain prevents me from walking more than 1 kilometre
- ☐ Pain prevents me from walking more than 500 metres
- ☐ I can only walk using a stick or crutches
- ☐ I am in bed most of the time

Section 5: Sitting

- ☐ I can sit in any chair as long as I like
- ☐ I can only sit in my favourite chair as long as I like
- ☐ Pain prevents me sitting more than one hour
- ☐ Pain prevents me from sitting more than 30 minutes
- ☐ Pain prevents me from sitting more than 10 minutes
- ☐ Pain prevents me from sitting at all

Section 6: Standing

- ☐ I can stand as long as I want without extra pain
- ☐ I can stand as long as I want but it gives me extra pain
- ☐ Pain prevents me from standing for more than 1 hour
- ☐ Pain prevents me from standing for more than 30 minutes
- ☐ Pain prevents me from standing for more than 10 minutes
- ☐ Pain prevents me from standing at all

Section 7: Sleeping

- ☐ My sleep is never disturbed by pain
- ☐ My sleep is occasionally disturbed by pain
- ☐ Because of pain I have less than 6 hours sleep
- ☐ Because of pain I have less than 4 hours sleep
- ☐ Because of pain I have less than 2 hours sleep
- ☐ Pain prevents me from sleeping at all

Section 8: Sex Life (if applicable)

- ☐ My sex life is normal and causes no extra pain
- ☐ My sex life is normal but causes some extra pain
- ☐ My sex life is nearly normal but is very painful
- ☐ My sex life is severely restricted by pain
- ☐ My sex life is nearly absent because of pain
- ☐ Pain prevents any sex life at all

Section 9: Social Life

- ☐ My social life is normal and gives me no extra pain
- ☐ My social life is normal but increases the degree of pain
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests e.g. sport
- ☐ Pain has restricted my social life and I do not go out as often
- ☐ Pain has restricted my social life to my home
- ☐ I have no social life because of pain

Section 10: Travelling

- ☐ I can travel anywhere without pain
- ☐ I can travel anywhere but it gives me extra pain
- ☐ Pain is bad but I manage journeys over two hours
- ☐ Pain restricts me to journeys of less than one hour
- ☐ Pain restricts me to short necessary journeys under 30 minutes
- ☐ Pain prevents me from travelling except to receive treatment

Score: / **x 100 =** **%**

Scoring: For each section the total possible score is 5: if the first statement is marked the section score = 0, if the last statement is marked it = 5. If all ten sections are completed the score is calculated as follows:

Example: 16 (total scored)
50 (total possible score) x 100 = 32%

If one section is missed or not applicable the score is calculated: 16 (total scored)
45 (total possible score) x 100 = 35.5%

Minimum Detectable Change (90% confidence): 10%points (Change of less than this may be attributable to error in the measurement)

Source: Fairbank JCT & Pynsent, PB (2000) The Oswestry Disability Index. *Spine*, 25(22):2940-2953.
Davidson M & Keating J (2001) A comparison of five low back disability questionnaires: reliability and responsiveness. Physical Therapy 2002;82:8-24.

*Note: Distances of 1mile, ½ mile and 100 yards have been replaced by metric distances in the Walking section.

Advisory Committee Briefing Materials: Available for Public Release

Appendix 2

Meta-Analysis of Efficacy and Safety of Extended- and Controlled-Release Opioids in Enriched Enrollment Randomized Withdrawal Trials

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ABSTRACT

Objective: The objective of this meta-analysis was to assess the efficacy and safety of hydrocodone extended-release (HC-ER) relative to other extended-release opioids in enriched enrollment randomized withdrawal (EERW) studies. **Methods:** We assessed three efficacy endpoints (change in pain intensity [PI] from randomization to Week 12, 30% response rates, and 50% response rates) and two safety endpoints (the percentage of patients with at least one AE and the percentage of patients who discontinued as a result of AEs) in both the pre- and post-randomization treatment periods. Fixed-effect and random-effects estimates (and 95% CIs) were calculated using the standard method for establishing the summary effect size for both continuous and binomial outcomes. **Results**: A literature search for opioid EERW studies in chronic pain identified 10 studies. These studies, plus data from an unpublished HC-ER EERW study, were included in the meta-analysis. All 11 studies were evaluable for pain intensity; 7 were evaluable for response rates; and 11 were evaluable for AEs. Using both a fixed- and random-effects model, the SES for active treatment was significantly superior to placebo when measured by pain intensity, 30% response rates, and 50% response rates; odds ratios for having an AE or discontinuing the trial due to an AE were significantly higher for active treatment relative to placebo. The CIs for pain intensity reduction, 30% response rates, and 50% response rates among all ER opioids studied overlapped, indicating no significant difference between opioids (oxymorphone, hydromorphone, oxycodone, morphine, tapentadol, buprenorphine, tramadol, and HC-ER). **Conclusion**: The efficacy and safety of HC-ER is similar to that of other ER opioids.

INTRODUCTION

Zogenix has recently completed a clinical trial of a new opioid analgesic, hydrocodone extended release (HC-ER). Hydrocodone is a full mu agonist opioid that has been available for decades, albeit only in combination with non-opioid analgesics (acetaminophen, ibuprofen), and is the most widely prescribed medication of any kind in the U.S. Full mu agonists are all regarded as having the same efficacy and overall safety, and differ primarily in *potency*, which refers to how many milligrams must be administered in order to produce a given effect. Nonetheless, it is reasonable to examine whether the efficacy and safety of HC-ER is similar to that of other pure mu agonist opioids, as would be expected.

The task of comparing treatments across trials is complicated by the fact that details of study design and study conduct influence the observed effect of any drug (Katz 2005; Katz 2008; Polydefkis 2008; Dworkin 2010; Dworkin 2012) – an issue so important that the FDA has launched an initiative called Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION), to develop an understanding of these relationships in order to improve design and conduct of future studies. Therefore, if a difference between two treatments (or even the same treatment) is seen in two different studies, it is usually unclear whether the difference is due to the treatments or to the study design and conduct.

To address the question of whether the efficacy of HC-ER is similar to that of other full mu agonist opioids, we performed a meta-analysis of published clinical trials of all such agents. In order to avoid the error of comparing treatments across study designs that are entirely different, we included only studies with enriched enrollment randomized withdrawal (EERW) designs (the same design as that of the HC-ER phase 3 study). An EERW study is a type of randomized, placebo-controlled study that includes a pre-randomization open-label period in which patients receive the active drug at a dose expected to provide therapeutic effects. Only patients who have an adequate response and tolerate the drug (according to preset criteria) are enrolled in the randomized blinded treatment period to receive active drug or placebo.

In order to ensure that the results for efficacy were robust, we compared these studies based on several different methods for quantifying pain intensity (PI) in common use: group mean differences, 30% responder rates, and 50% responder rates. In addition, we compared safety across studies.

METHODS

1. Literature Search

We conducted two searches to find published articles of clinical studies using an EERW study design evaluating the analgesic efficacy and safety of systemic (oral or transdermal) opioids for any type of chronic pain.

An initial search was conducted in PubMed using the following search algorithm: “(enriched enrollment OR withdrawal) AND (randomized) AND (opioid OR narcotic) AND (pain) AND (study OR trial) NOT (epidural OR intrathecal OR subcutaneous OR injection OR intravenous) AND English[Language]”. We

also conducted a second search by reviewing the citations in four reviews we had on file (Furlan 2011; Katz 2009; McQuay 2008; and Quessy 2010) for relevant original articles. All titles and relevant abstracts were individually screened. Studies were excluded if they involved (i) acute or postoperative pain or breakthrough pain; (ii) detoxification; (iii) NSAIDs; (iv) animals; (v) pharmacokinetics; (vi) pediatric patients; (vii) assessment of withdrawal symptoms of opioids but not using an EERW design; (viii) lack of a placebo-controlled arm; (ix) follow-up in the postrandomization period of less than 12 weeks.

2. Efficacy Data

A meta-analysis was conducted for those studies in which the data were available on any of the three efficacy endpoints: (i) Change in PI from randomization to Week 12, (ii) response rate of ≥30%, and (iii) response rate of ≥50%. Response rates were measured from the pre-treatment baseline to Week 12. A 30% response is generally defined as having a ≥30% decrease in PI from pretreatment to endpoint (Week 12 in this case). A 50% response is defined as having a ≥50% decrease in PI from pretreatment to endpoint (Week 12 in this case). The cutoff of 30% and 50% response is a widely used cutoff in analgesic trial (Dworkin 2008).

Fixed-effect and random-effects estimates (and 95% CIs) were calculated using the standard method for establishing the summary effect size as described in Borenstein et al. (2009) for both continuous and binomial outcomes. For the fixed-effect model, the assumption is that the true effect is the same across all studies. In contrast, for the random-effects model, the assumption is that the effect size is similar but not the same across all studies as a result of key differences such as different study populations and or the specific type of opioid studied.

For the continuous variable, change in PI, Hedges' g was calculated to establish an unbiased standardized effect size to account for the bias in the pooled treatment effect estimate (Hedges 1981) with the mean and 95% confidence intervals (CIs). A positive Hedges' g suggests that the efficacy of the active treatment is superior to that of the placebo. A negative Hedges' g suggests that the efficacy of the active treatment is less than that of the placebo.

For response rates, a separate meta-analysis was conducted for each endpoint to estimate the summary odds ratio (OR) and 95% CI. An OR >1 indicates that the odds of having a response in the active treatment group are better than in the placebo group. An OR <1 indicates that the odds of having a response in the active treatment group are less than in the placebo group.

3. Safety Data

Each study included in the efficacy meta-analysis was reviewed for the incidence of adverse events (AEs). Opioid withdrawal was considered an AE and was included in all AE calculations. Although each study's post-randomization period was 12 weeks in duration, the pre-randomization period differed between studies in terms of length and titration approach. No adjustment was made for the difference in duration between studies of the pre-randomization period.

For the pre-randomization period, we collected the following data: (i) the percentage of patients with at least one AE in the pre-randomization period, and (ii) the percentage of patients who discontinued the pre-randomization period as a result of AEs.

For the post-randomization treatment period and for each treatment group (active and placebo), the following safety indicators were calculated: (i) the percentage of patients with at least one AE, and (ii) the percentage of patients discontinuing as result of the AE. The summary OR and 95% CI were estimated for each study. The summary OR estimates the chance of having at least one AE (or discontinuing due to an AE) in the active treatment group compared to the placebo group.

Fixed-effect and random-effects estimates (and 95% CIs) were calculated using the same statistical methods as the efficacy outcomes.

RESULTS

1. Search Results and Studies Included in the Meta-Analysis

The initial search yielded 79 articles, 10 of which were considered relevant: 2 articles were reviews (Furlan 2011; Katz 2009) and 8 were original articles (Steiner 2011; Friedman 2011; Schwartz 2011; Katz 2010; Hale 2010; Peniston 2009; Landau 2007; and Katz 2007). The second search yielded 11 additional relevant articles (after removing duplicates): Hale 2005; Hale 2007; Russell 2000; Vorsanger 2008; Burch 2007; Caldwell 1999; Galer 2005; Poulain 2008; Vondrackova 2008; Kongsgaard 1998; Schnitzer 2000.

Of the total 17 articles retrieved (8 from the initial search + 11 from the additional search), 10 had a PI endpoint at Week 12, and 7 had the PI endpoints collected at various timepoints. In order to perform a meta-analysis of efficacy, we needed to use studies using the same timepoint for the collection of PI data. Thus, we selected for the meta-analysis the 10 studies that collected the PI data at Week 12: Burch 2007; Friedman 2011; Hale 2007; Hale 2010; Katz 2010; Katz 2007; Peniston 2009; Schwartz 2011; Steiner 2011; Vorsanger 2008. An unpublished clinical study conducted by Zogenix was added to the meta-analysis (Zogenix 2012). Thus, a total of 11 studies were included in the meta-analysis. The opioids evaluated in these 11 studies were: oxymorphone in 3 studies, tramadol in 2 studies, and hydrocodone, buprenorphine, morphine, hydromorphone, tapentadol, and oxycodone in one study each.

2. Analysis of the PI Efficacy Endpoints

The PI data (change in PI from randomization to Week 12) for each of the 11 individual studies are presented in Table 1. As has been observed before, in most studies the pain scores increased in both the active group and placebo groups (change from baseline in PI yields a positive value), but it increased more with placebo (Table 1). These data were used to calculate the SES of active treatment versus placebo in each study. SES values (and associated 95% CIs) are plotted by study and for all studies combined in Figure 1. The SES for the PI endpoint was 0.38 (95%CI: 0.32 to 0.45; fixed effect) or 0.39 (95%CI: 0.31 to 0.47; random effect) for all 11 studies combined, showing a statistically significant overall superiority of the efficacy of active opioid analgesic treatments versus placebo in these trials.

In all studies except one (Friedman 2011), the efficacy of active treatment was statistically significantly superior to that of placebo. In these studies the SES ranged from 1.0 [95%CI: 0.06 to 1.35] to 0.18 [95% CI: 0.04 to 0.46], with all upper bounds of 95%CI being positive; for the Friedman 2011 study, the SES was 0.18 [95% CI: -0.02 to 0.37]. With an SES of 0.31 (95%CI: 0.08 to 0.53), the effect size of HC-ER in the Zogenix study as measured by mean PI was on par with that of all combined studies (SES = 0.38).

A subgroup analysis by opioid was not conducted; however, in the 3 studies evaluating oxymorphone (Hale 2007; Katz 2007; Peniston 2009), the SESs ranged from 0.53 to 1.0. This observation suggests that differences in SES between the studies are likely to be more a function of the study design than of the type of opioid itself.

Table 1. Efficacy data from individual studies

		Active Treatment			Placebo		
Reference	**Opioid Evaluated**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**
Burch 2007[a]	Tramadol	-3.03	2.12	393	-2.29	1.97	196
Friedmann 2011	Oxycodone	-0.70	2.05	203	-0.30	2.48	207
Hale 2007[b,c]	Oxymorphone	8.70	20.0	70	31.6	25.0	72
Hale 2010[c]	Hydromorphone	0.40	2.00	133	1.20	2.50	133
Katz 2010	Morphine	-0.20	1.90	170	0.30	2.10	173
Katz 2007[b]	Oxymorphone	10.9	24.5	105	26.0	27.9	100
Peniston 2009[b,c]	Oxymorphone	0.10	20.0	174	12.1	25.0	169
Schwartz 2011[c]	Tapentadol	0.00	2.00	196	1.40	2.50	192
Steiner 2011[c]	Buprenorphine	1.21	2.00	256	1.79	2.50	283
Vorsanger 2008[b,c]	Tramadol	5.20	20.0	127	12.20	25.0	126
Zogenix 2011	Hydrocodone	0.48	1.56	151	0.96	1.55	151

Data are mean (SD) change in PI from randomization to Week 12, unless otherwise noted. N are post-randomization number of patients. Most studies used the LOCF imputation; however, any differences in the denominators of pain intensity at week 12 appear to be due to analysis on incomplete Week 12 response imputations that were not fully described in the articles.
(a) Mean change in PI from pretreatment baseline, not randomization, to week 12
(b) PI measured from 0 to 100.
(c) SD imputed for active treatment (2.0) and placebo (2.5), and 20 and 25, respectively, for PI scales from 0 to 100.
SD = standard deviation; PI = pain intensity;

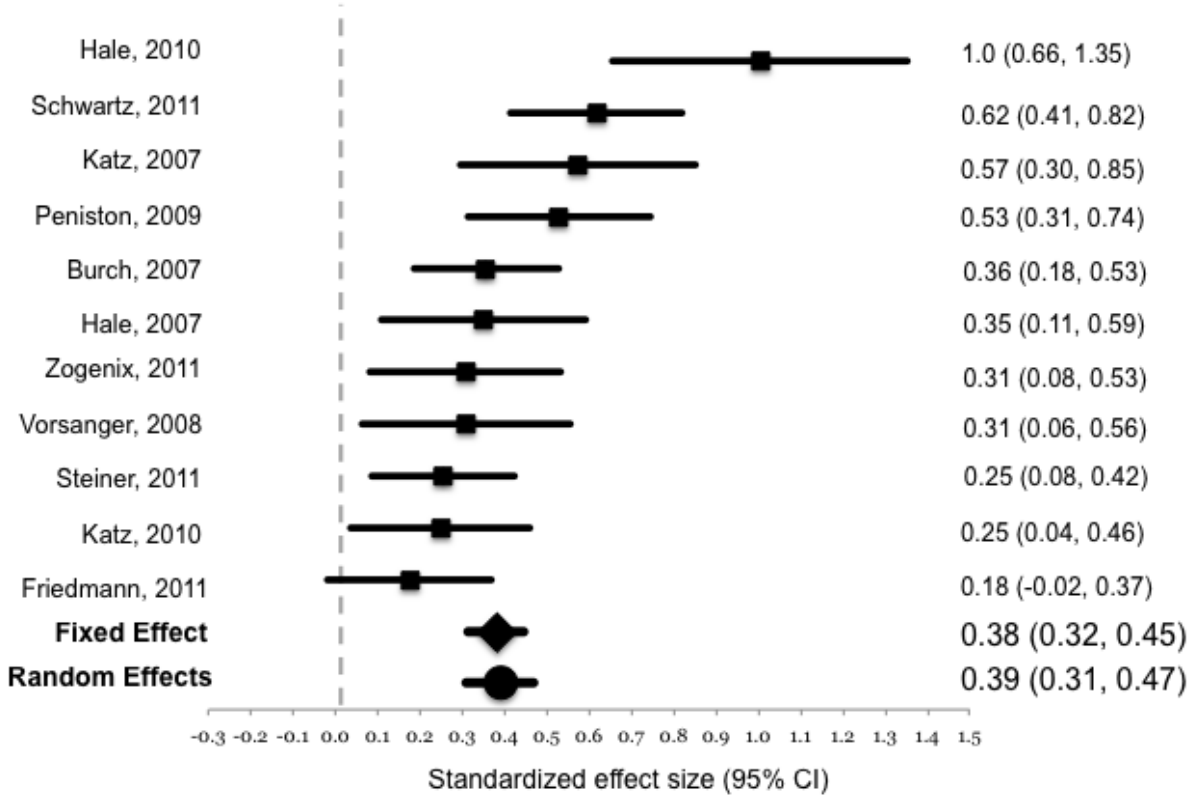

Figure 1. SES plots for the pain efficacy endpoint of change in PI from randomization to Week 12. A SES>0 indicates that the active treatment has a greater effect than placebo.

3. Analysis of the Responder Rate Endpoints

The responder rates (30% response and 50% response; defined as a 30% or 50% decrease in PI from pretreatment to Week 12) are presented in Table 1 for the 7 individual studies in which response rate data were available. These data were used to calculate the OR for having a 30% or 50% response while on active treatment versus on placebo. The ORs (and associated 95% CIs) are plotted by study and for all studies combined in Figure 2. Data for all 7 studies combined showed that patients on active treatment were 2.03 times (95%CI: 1.73 to 2.38; fixed effect) or 1.91 times (95%CI: 1.42 to 2.57; random effect) more likely to have a 30% response than those on placebo (statistically significant). Patients on active treatment were also 1.97 times more likely to have a 50% response than those on placebo (95%CI: 1.68 to 2.32 for fixed effect; 95%CI: 1.39 to 2.79 for random effect; statistically significant). By study, OR ranged from 4.6 (95%CI: 2.8 to 7.5) in the Zogenix 2011 study to 1.6 (95%CI: 1.1 to 2.4) in the Schwartz 2011 study for the 30% response (Fig. 2A), and from 3.9 (95%CI: 2.2 to 7.1) in Katz 2007 study to 1.5 (95%CI: 0.96 to 2.3) in Katz 2010 study for the 50% response. The OR for having a 30% or 50% response with HC-ER in the Zogenix study was 4.6 [95%CI: 2.8 to 7.5] and 3.0 [95%CI: 1.8 to 5.0], respectively.

Table 2. Responder rates in individual studies

		30% Response[a]		50% Response[a]	
		Active Treatment	Placebo	Active Treatment	Placebo
	Opioid Evaluated	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Burch 2007	Tramadol	322/428 (75.2)	134/211 (63.5)	183/406 (45.1)	61/203 (30.0)
Hale 2010	Hydromorphone	80/133 (60.2)	57/133 (42.9)	56/133 (42.1)	32/133 (24.1)
Katz 2010	Morphine	124/170 (72.9)	100/173 (57.8)	97/170 (57.1)	82/173 (47.4)
Katz 2007[b]	Oxymorphone	66/105 (62.9)	34/100 (34.0)	61/105 (58.1)	26/100 (26.0)
Schwartz 2011	Tapentadol	105/196 (53.6)	81/192 (42.2)	74/196 (37.8)	53/192 (27.6)
Steiner 2011	Buprenorphine	164/256 (64.1)	150/283 (53.0)	136/256 (53.1)	113/283 (39.9)
Zogenix 2011	Hydrocodone	102/151 (67.5)	47/151 (31.1)	72/151 (47.7)	35/151 (23.2)

(a) A 30% response is defined as having a ≥30% decrease in PI pretreatment baseline to Week 12. A 50% response is defined as having a ≥50% decrease in PI from pretreatment baseline to Week 12. All studies used LOCF imputation.
(b) Response rate at 12 weeks reported only for patients with 12-week data, i.e. no LOCF. In an attempt to be more consistent with other studies, missing was imputed as a failure.

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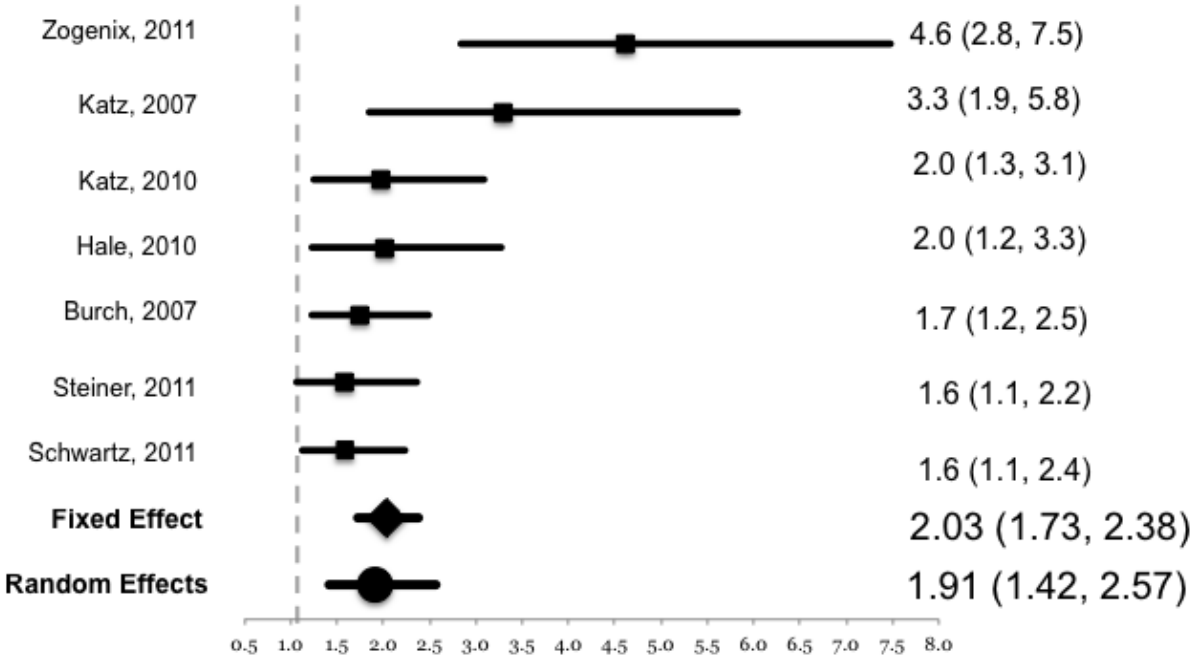

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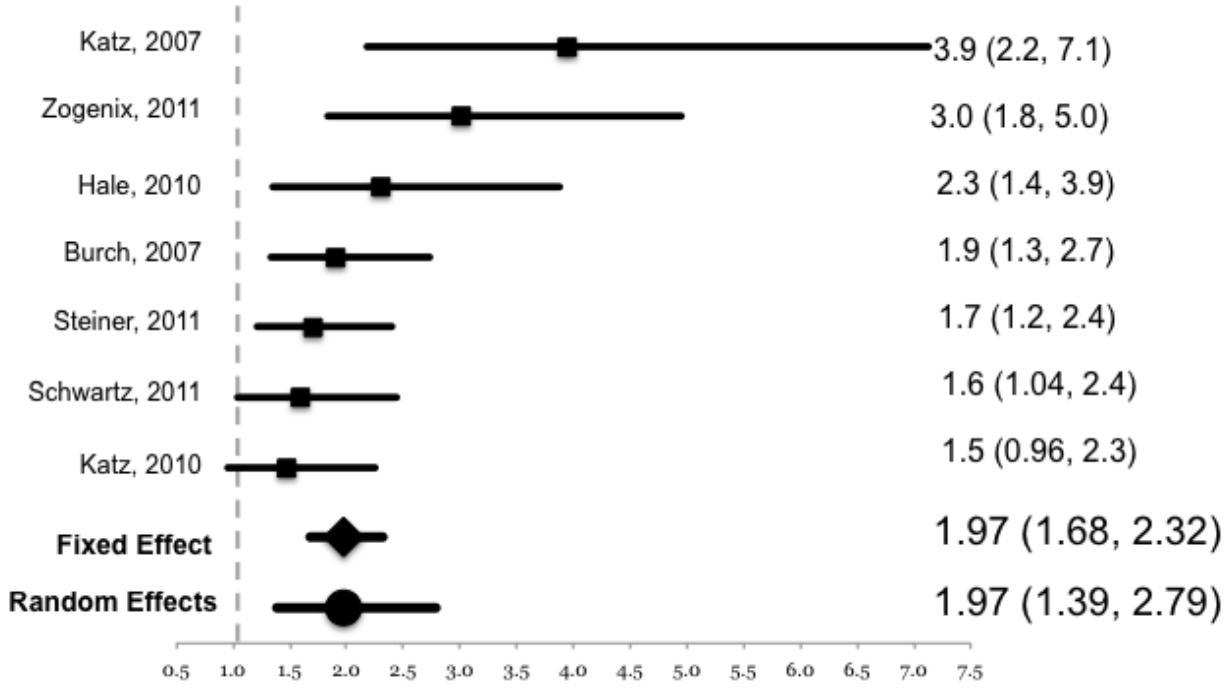

Figure 2. Odds ratios for responder rates. A. 30% response. B. 50% response. An OR >1 indicates a higher likelihood of having a response while on active treatment compared to placebo.

4. Meta-Analysis of Safety

The percentage of patients with at least one AE and the percentage of patients discontinuing due to an AE in the pre-randomization and randomization phases are presented in Table 3. These data were used to calculate the OR for having at least one AE and for discontinuing due to AEs while on active treatment versus on placebo. The ORs (and associated 95% CIs) are plotted by study and for all studies combined in Figure 3.

Overall, in the 11 studies combined, patients on active treatment were statistically significantly more likely to have at least one AE than those on placebo (OR = 2.03 [95%CI: 1.73 to 2.38; fixed effect; 1.52 [95%CI: 1.04 to 2.22] random effect). The OR for individual studies ranged from 0.8 (95%CI: 0.5 to 1.2) in the Hale 2010 study to 2.4 (95%CI: 1.4 to 4.1) in the Vorsanger 2008 study. For 4 studies, the likelihood of having an AE while on active or on placebo was not statistically significantly different (95%CIs included 1).

Overall, in the 11 studies combined, patients on active treatment were statistically significantly more likely to discontinue due to an AE than those on placebo (OR = 1.81 [95%CI: 1.44 to 2.28] fixed effect; 1.53 [95%CI: 0.96 to 2.45] random effect). The OR for individual studies ranged from 0.16 (95%CI: 0.03 to 0.71) for the Zogenix 2011 study to 6.00 (95%CI: 3.15 to 11.44) for the Burch 2007 study; for 6 studies the likelihood of discontinuing due to an AE while on active treatment or on placebo was not statistically significantly different (95%CIs included 1). The Zogenix 2011 study was the only study in which patients in the active treatment group were statistically significantly less likely to discontinue due to an AE than those in the placebo group (OR = 0.16 [95%CI: 0.03 to 0.71]).

Table 3. Incidence of AEs and AEs leading to discontinuation in individual studies

		Patients with at least one AE			Patients discontinuing due to an AE		
		Pre-Randomization	Post-randomization		Pre-Randomization	Post-randomization	
Reference	Opioid Evaluated	n/N (%)	Active n/N (%)	Placebo n/N (%)	n/N (%)	Active n/N (%)	Placebo n/N (%)
Burch 2007	Tramadol	NR	NR	NR	225/381 (59.1)	106/432 (24.5)	11/214 (5.1)
Friedmann 2011	Oxycodone	NR	NR	NR	124/146 (84.9)	43/205 (21.0)	22/207 (10.6)
Hale 2007	Oxymorphone	174/250 (69.6)	31/70 (44.3)	27/73 (37.0)	47/101 (46.5)	7/70 (10.0)	8/73 (11.0)
Hale 2010	Hydromorphone	247/459 (55.3)	64/134 (47.8)	73/134 (54.5)	60/191 (31.4)	9/134 (6.7)	4/134 (3.0)
Katz 2010	Morphine	347/547 (63.4)	91/171 (53.2)	84/173 (48.6)	124/203 (22.7)	18/171 (10.5)	13/173 (7.5)
Katz 2007	Oxymorphone	224/325 (68.9)	61/105 (58.1)	44/100 (44.0)	59/120 (49.2)	9/105 (8.6)	8/100 (8.0)
Peniston, 2009	Oxymorphone	NR	45/175 (25.7)	28/172 (16.3)	106/227 (46.7)	16/174 (9.2)	15/169 (8.9)
Schwartz, 2011	Tapentadol	417/588 (70.9)	139/196 (70.9)	100/193 (51.8)	100/196 (51.0)	29/63 (46.0)	15/62 (24.2)
Steiner, 2011	Buprenorphine	563/1024 (55.0)	141/257 (54.8)	148/284 (52.1)	239/483 (49.5)	40/256 (15.6)	20/283 (7.1)
Vorsanger, 2008	Tramadol	499/619 (80.6)	97/128 (75.8)	72/127 (56.7)	128/233 (54.9)	13/128 (10.2)	18/127 (14.2)
Zogenix, 2011	Hydrocodone	270/510 (52.9)	91/151 (60.3)	67/151 (44.4)	47/208 (22.6)	2/151 (1.3)	12/151 (7.9)

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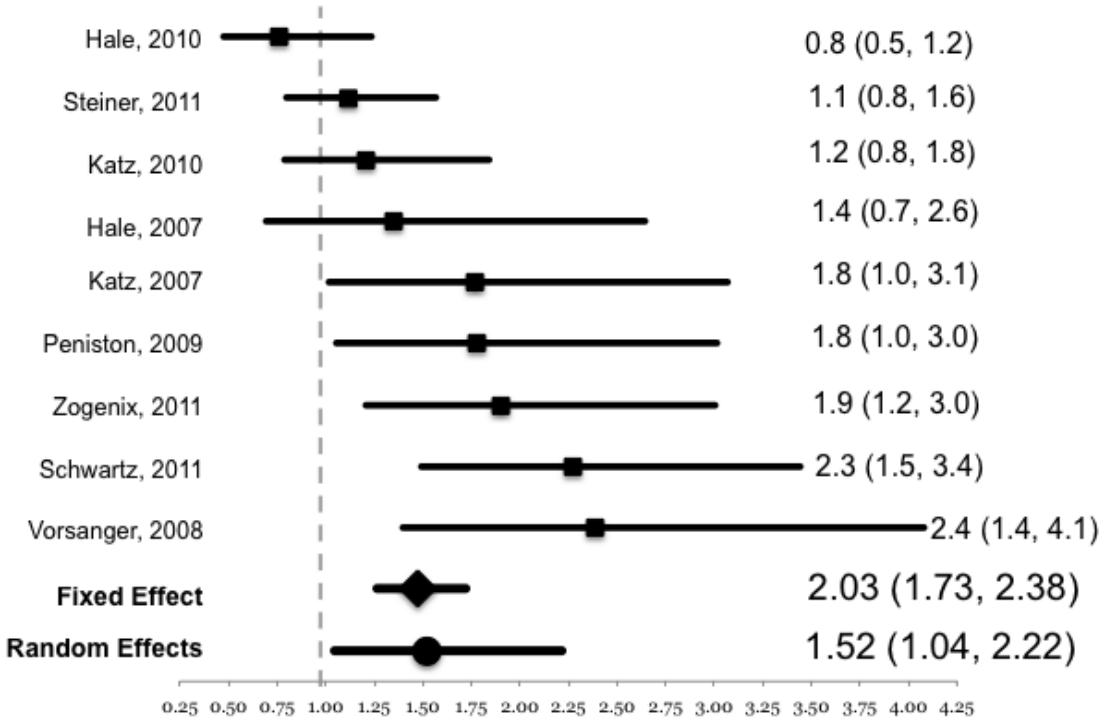

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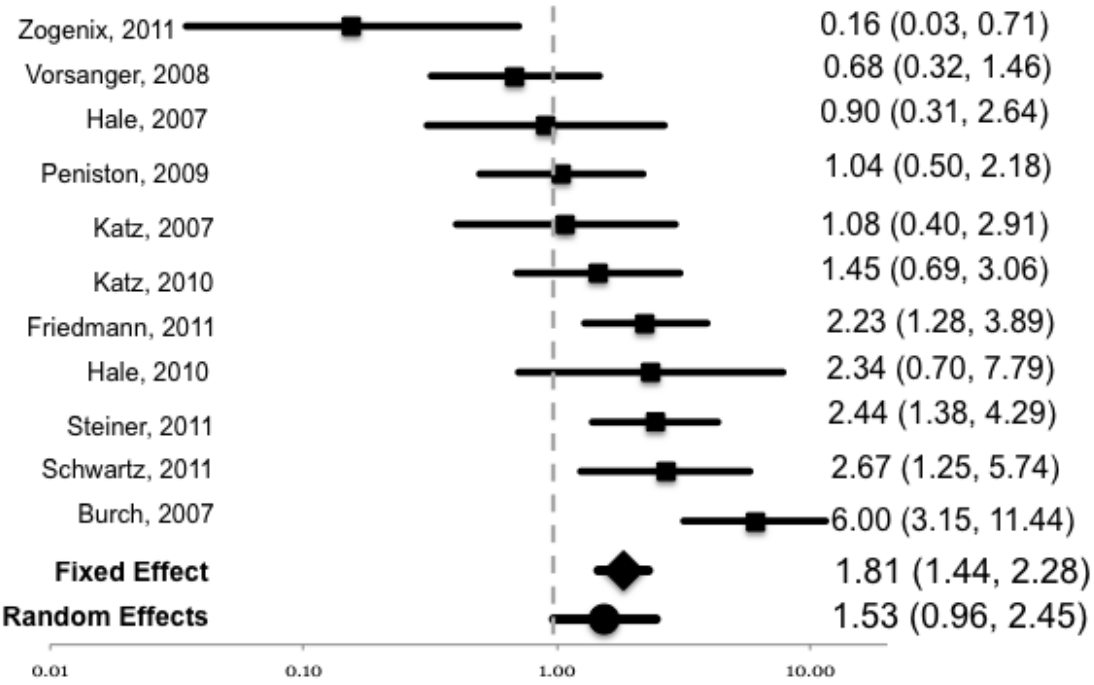


Figure 3. Odds ratios for safety outcomes in the post-randomization period. A. Incidence of at least one AE. B. Incidence of discontinuation due to an AE. OR >1 indicate a higher likelihood of having an event

while on active treatment compared to placebo.

CONCLUSIONS

The efficacy of all the extended-release opioids, when examined with studies of similar design, is within the same range. This is the case whether efficacy is evaluated looking at mean PI, 30% responder rates, or 50% responder rates. This is not surprising since all full mu agonists have the same pharmacological effects. Our results are in agreement with those of another meta-analysis of opioids for chronic pain, conducted by Furlan and colleagues, which concluded that there is no substantial difference between types of opioids and analgesic potency (strong vs. weak opioids) (Furlan 2011) (Furlan's analysis was only performed on the PI endpoint, not on the response rate).

Nevertheless, in some studies the effect size of the active treatment versus placebo appeared higher than that for all studies combined: Hale 2010 (hydromorphone) for the change in PI endpoint, and Zogenix 2011 (HC-ER) and Katz 2007 (oxymorphone) for the responder rates endpoint. Interestingly, the efficacy of HC-ER in the Zogenix 2011 study was within the average of all studies combined for the PI endpoint but was higher than other studies for the responder rate endpoint. This finding suggests that the numerical rankings of "efficacy" of mu agonist opioids across clinical trials is not robust when using different methods of PI, and supports the use of different approaches to measuring efficacy, and that all these approaches need to be considered when conducting meta-analyses. Otherwise differences in observed "efficacy" across studies can be falsely attributed to drug differences when they are more likely due to differences in study design and conduct. Although all studies included in this meta-analysis were EERW designs, these studies still differ in important features of study design (such as inclusion/exclusion criteria, criteria for randomization, method of conversion and titration, use of concomitant analgesics, etc.). Studies also differ substantially in study conduct, which unfortunately is rarely described in detail in publications. Also the imputation method for efficacy data varies by study and is sometimes not clearly described in the publications. Regarding safety, the overall picture showed, unsurprisingly, that patients on active treatment generally have a greater chance of having an AE and to be discontinued due to an AE.

In conclusion, the efficacy and safety of HC-ER, when evaluated on a variety of measures, is within the expected norms of other extended-release opioids.

REFERENCES

1. Katz N. Methodological issues in clinical trials of opioids for chronic pain. Neurology. 2005;65(12 Suppl 4):S32-49.
2. Katz J, Finnerup NB, Dworkin RH. Clinical trial outcome in neuropathic pain: relationship to study characteristics. Neurology. 2008;70(4):263-72.
3. Polydefkis M, Raja SN. What can we learn from failed neuropathic pain trials? Neurology. 2008;70(4):250-1.
4. Dworkin RH, Turk DC, Peirce-Sandner S, Baron R, Bellamy N, Burke LB, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain. 2010;149(2):177-93
5. Dworkin RH, Turk DC, Peirce-Sandner S, Burke LB, Farrar JT, Gilron I et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain. 2012;153(6):1148-58.
6. Zogenix Inc. A randomized double-blind, placebo-controlled trial to evaluate the efficacy, tolerability and safety of hydrocodone bitartrate extended-release capsules in opioid-experienced subjects with moderate to severe chronic low back pain. Clinical Study Report ZX002-0801. 2011.
7. Furlan A, Chaparro LE, Irvin E, Mailis-Gagnon A. A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. Pain Res Manag. 2011;16(5):337-51.
8. Katz N. Enriched enrollment randomized withdrawal trial designs of analgesics: focus on methodology. Clin J Pain. 2009;25(9):797-807.
9. McQuay HJ, Derry S, Moore RA, Poulain P, Legout V. Enriched enrolment with randomised withdrawal (EERW): Time for a new look at clinical trial design in chronic pain. Pain. 2008;135(3):217-20.
10. Quessy SN. Two-stage enriched enrolment pain trials: a brief review of designs and opportunities for broader application. Pain. 2010;148(1):8-13.
11. Steiner DJ, Sitar S, Wen W, Sawyerr G, Munera C, Ripa SR, Landau C. Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naïve patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage. 2011;42(6):903-17.
12. Friedmann N, Klutzaritz V, Webster L. Efficacy and safety of an extended-release oxycodone (Remoxy) formulation in patients with moderate to severe osteoarthritic pain. J Opioid Manag. 2011;7(3):193-202.
13. Schwartz S, Etropolski M, Shapiro DY, Okamoto A, Lange R, Haeussler J, Rauschkolb C. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin. 2011;27(1):151-62.
14. Katz N, Hale M, Morris D, Stauffer J. Morphine sulfate and naltrexone hydrochloride extended release capsules in patients with chronic osteoarthritis pain. Postgrad Med. 2010;122(4):112-28.
15. Hale M, Khan A, Kutch M, Li S. Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. Curr Med Res Opin. 2010;26(6):1505-18.

16. Peniston JH, Gould E. Oxymorphone extended release for the treatment of chronic low back pain: a retrospective pooled analysis of enriched-enrollment clinical trial data stratified according to age, sex, and prior opioid use. Clin Ther. 2009;31(2):347-59.
17. Landau CJ, Carr WD, Razzetti AJ, Sessler NE, Munera C, Ripa SR. Buprenorphine transdermal delivery system in adults with persistent noncancer-related pain syndromes who require opioid therapy: a multicenter, 5-week run-in and randomized, double-blind maintenance-of-analgesia study. Clin Ther. 2007;29(10):2179-93.
18. Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R, Podolsky G. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. Curr Med Res Opin. 2007;23(1):117-28.
19. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. J Pain. 2005;6(1):21-8.
20. Hale ME, Ahdieh H, Ma T, Rauck R; Oxymorphone ER Study Group 1. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. J Pain. 2007;8(2):175-84.
21. Russell I, Kamin M, Bennett R, et al. Efficacy of tramadol in treatment of pain in fibromyalgia. J Clin Rheumatol. 2000; 6:250–257.
22. Vorsanger GJ, Xiang J, Gana TJ, Pascual ML, Fleming RR. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. J Opioid Manag. 2008;4(2):87-97.
23. Burch F, Fishman R, Messina N, Corser B, Radulescu F, Sarbu A, Craciun-Nicodin MM, Chiriac R, Beaulieu A, Rodrigues J, Beignot-Devalmont P, Duplan A, Robertson S, Fortier L, Bouchard S. J A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. Pain Symptom Manage. 2007;34(3):328-38.
24. Caldwell JR, Hale ME, Boyd RE, Hague JM, Iwan T, Shi M, Lacouture PG. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol. 1999;26(4):862-9.
25. Galer BS, Lee D, Ma T, Nagle B, Schlagheck TG. MorphiDex (morphine sulfate/ dextromethorphan hydrobromide combination) in the treatment of chronic pain: three multicenter, randomized, double-blind, controlled clinical trials fail to demonstrate enhanced opioid analgesia or reduction in tolerance. Pain 2005;115:284–95.
26. Poulain P, Denier W, Douma J, Hoerauf K, Samija M, Sopata M, Wolfram G. Efficacy and safety of transdermal buprenorphine: a randomized, placebo-controlled trial in 289 patients with severe cancer pain. J Pain Symptom Manage 2008;36:117–25.
27. Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, Ruckes C, Weber S, Grothe B, Fleischer W, Reimer K. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. J Pain 2008;9:1144–54.
28. Kongsgaard UE, Poulain P. Transdermal fentanyl for pain placebo in adults with chronic cancer pain. Eur J Pain. 1998;2(1):53-62.
29. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. J Rheumatol. 2000;27(3):772-8.

30. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. J Education Stat 1981:6;107-28.
31. Borenstein M, Hedges LV, Jiggins, JPT, and Rothstein HR. Introduction to meta-analysis. Wiley, Chichester, U.K. 2009.

Appendix 3: Zohydro Medication Guide

Medication Guide *DRAFT*
Zohydro™ (zoh-hye-droh) (hydrocodone bitartrate) CII
Extended-Release Capsules
(10 mg, 15 mg, 20 mg, 30 mg, 40 mg and 50 mg)

This Medication Guide has been approved by the U.S. FDA
Issue: DATE

What is the most important information I should know about Zohydro?

- Zohydro can cause trouble breathing if used incorrectly. The breathing problems can even lead to death. Follow your healthcare provider's directions exactly.
- **Zohydro capsules must be swallowed whole and should never be crushed, chewed or dissolved.** Chewing, crushing or dissolving Zohydro capsules could cause death from overdose.
- **Do not consume alcohol while taking Zohydro.** Even other medicines that may or may not require a prescription, such as cough medicines, can have alcohol in them. Alcohol can increase the risk of overdose and may lead to death.

What is Zohydro?

- Zohydro is a prescription medicine that contains the opioid (narcotic) pain medicine hydrocodone. It is used to treat moderate to severe pain.
- Zohydro is for patients who have constant pain that is expected to last for a long time. It is not for pain that occurs only once in a while.
- **Zohydro is a federally controlled substance (CII).** This is because it contains a strong opioid medicine that some people may abuse. **Selling or giving away Zohydro is against the law.**

Who should not take Zohydro?

Do not take Zohydro if you:

- are having an asthma attack or have severe asthma, trouble breathing, or other lung problems.
- have a bowel blockage or obstruction (paralytic ileus)

- **What should I tell my healthcare provider before taking Zohydro?**
- **Tell your healthcare provider if you have a history of:**
- trouble breathing or any lung problems
- liver disease
- low blood pressure
- head injury or brain problems
- severe kidney disease
- seizures
- symptoms of constipation or blocked bowels
- thyroid problems
- a disease that affects your gallbladder or pancreas such as pancreatitis
- a condition that affects your adrenal gland, such as Addison's disease
- an enlarged prostate or problems urinating
- abuse of medications or street drugs, alcohol addiction, or mental health problems. Your chance of being addicted to Zohydro is increased.

Tell your healthcare provider if you:

- **are pregnant or planning to become pregnant.**
- **are breastfeeding.** Some hydrocodone passes into breast milk and may harm your baby.
- are taking prescription, over the counter medicines, vitamins or herbal supplements.
- are taking medicines that treat infections or depression.

Be especially careful about taking other medicines that make you sleepy such as:

- other pain medicines
- sleeping pills
- medicines for anxiety
- tranquilizers
- antihistamines
- medicines for nausea
- antidepressants
- muscle relaxants

Do not start taking any medicines while using Zohydro without talking to your healthcare provider first.

How should I take Zohydro?

- Do not change your dose. Take Zohydro exactly as prescribed by your healthcare provider.
- **Zohydro capsules must be swallowed whole and should never be crushed, chewed or dissolved.** Taking chewed, crushed or dissolved Zohydro capsules is very dangerous. You could die from an overdose of the medicine.
- Your healthcare provider may change your dose depending on your reactions to the medicine. Do not change your dose unless your healthcare provider tells you to change it. Do not take Zohydro more often than prescribed.
- Talk with your healthcare provider regularly about your pain. Your healthcare provider can decide if you still need Zohydro, or if you need a different dose.
- **Do not stop taking Zohydro without talking to your healthcare provider**. If you stop taking Zohydro suddenly, you may have withdrawal symptoms such as: nausea, vomiting, stomach cramping, chills, sweating, anxiety, muscle pain.

How do I dispose of unused Zohydro?

- After you stop taking Zohydro, flush unused product down the toilet, unless otherwise directed.

What should I avoid while taking Zohydro?

- **Do not drink alcohol or use prescription or over the counter medicines that contain alcohol.** Using alcohol while taking Zohydro can increase your risk of having an overdose and may lead to death.
- **Do not drive or operate heavy machinery**, until you know how Zohydro affects you. Zohydro can make you sleepy, dizzy, or lightheaded.

What are the possible side effects of Zohydro?

The most common side effects of Zohydro include:

- constipation
- nausea
- vomiting
- light-headedness
- dizziness
- headache
- drowsiness or sleepiness

Call your healthcare provider if you have any of the symptoms listed below:

- severe dizziness
- severe constipation
- severe vomiting
- abdominal pain, or abdominal bloating

Get emergency medical help if you have:

- trouble breathing or shortness of breath
- extreme drowsiness, feel faint, confused
- abnormal heart beat problems
- **allergic reactions** such as: trouble breathing, pounding heart beat, chest pain, swelling of the face tongue or throat

These are not all the possible side effects of Zohydro. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088**.**

For more information go to www.FDA.gov

For more information about Zohydro go to zohydrorems.com or call 1-866-ZOGENIX.

Manufactured by: Alkermes Gainesville LLC, Gainesville, GA.

Manufactured for: Zogenix, Inc., San Diego, CA

Appendix 4: Patient Counseling Document

Patient Counseling Document on Extended-Release / Long-Acting Opioids
Patient Name:
The DOs and DON'Ts of Extended-Release / Long - Acting Opioids
DO: • Read the **Medication Guide** • Take your medicine exactly as prescribed • Store your medicine away from children and in a safe place • Flush unused medicine down the toilet • Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
Call 911 or your local emergency service right away if: • You take too much medicine • You have trouble breathing, or shortness of breath • A child has taken this medicine
Talk to your healthcare provider: • If the dose you are taking does not control your pain • About any side effects you may be having • About all the medicines you take including over-the-counter medicines, vitamins, and dietary supplements
DON'T: • **Do not** give your medicine to others • **Do not** take medicine unless it was prescribed for you • **Do not** stop taking your medicine without talking to your healthcare provider • **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider. • **Do not** drink alcohol while taking this medicine
For additional information on your medicine go to: **dailymed.nlm.nih.gov**

Patient Counseling Document on Extended-Release / Long-Acting Opioids
Patient Name:
Patient Specific Information
Take this card with you every time you see your healthcare provider and tell him/her: • Your complete medical and family history, including any history of substance abuse or mental illness • The cause, severity, and nature of your pain • Your treatment goals • All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements • Any side effects you may be having **Take your opioid pain medicine exactly as prescribed by your healthcare provider.**

Initial REMS Approval: mm/yyyy

PROPOSED EXTENDED-RELEASE (ER) AND LONG-ACTING (LA) OPIOIDS RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Advisory Committee Briefing Materials: Available for Public Release

I. GOAL:

Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse and abuse of extended-release (ER) and long-acting (LA) opioids (collectively referred to as ER/LA opioids) while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

II. REMS ELEMENTS:

A. Medication Guide

A Medication Guide will be dispensed with each ER/LA opioid prescription in accordance with 21 CFR § 208.24.

The Medication Guides for ER/LA opioids are part of the ER/LA opioid REMS program and will be available on the ER/LA opioids REMS website (www.ER-LA-opioidREMS.com).

B. Elements To Assure Safe Use

1. Training will be made available to healthcare providers who prescribe ER/LA opioids.
    a. The NDA/ANDA holders of ER/LA opioid products ("NDA/ANDA holders") will ensure that training is made available to healthcare providers who prescribe ER/LA opioids.
        i. The content of the training will be based on the learning objectives established by FDA, in FDA's Blueprint for Prescriber Education for the Extended-Release/Long-Acting opioid Class-wide REMS (FDA Blueprint). The FDA Blueprint contains core messages about the safe use and risks of ER/LA opioids.
        ii. The training will be developed and conducted by accredited, independent continuing education (CE) providers, under educational grants provided by the NDA/ANDA holders. NDA/ANDA holders will not have input on the content of the training, and instead NDA/ANDA holders will refer CE providers to the FDA Blueprint posted on the FDA's website, www.xxxx.fda.gov.
        iii. The training must include a knowledge assessment and proof of successful program completion.

iv. NDA/ANDA holders will maintain, on the ER/LA opioid REMS website (www.ER-LA-opioidREMS.com), a current list of accredited CE programs supported by educational grants from the NDA/ANDA holders that meet the requirements of the ER/LA Opioid REMS.

v. NDA/ANDA holders will ensure that an independent audit of the CE providers' educational materials (supported by educational grants from the NDA/ANDA holders) is conducted to evaluate the quality of the CE content against the FDA Blueprint as well as against the Accreditation Council for Continuing Medical Education (ACCME) standards for CE.

b. NDA/ANDA holders will ensure that a copy of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is provided to prescribers; the PCD can be used by prescribers to counsel patients on the risks and safe use of ER/LA opioids that are common to all ER/LA opioid products.

i. NDA/ANDA holders will make the PCD available on the ER/LA Opioid REMS website (www.ER-LA-opioidREMS.com), and will provide it to prescribers, upon request.

ii. Information regarding ordering copies of the PCD can be found on the ER/LA opioid REMS website (www.ER-LA-opioidREMS.com).

c. NDA/ANDA holders will ensure that within 30 calendar days of the availability of the first prescriber training, as described in B.1.a above, the Dear Healthcare Professional Letter will be sent to all prescribers who are registered with Drug Enforcement Administration (DEA) to prescribe Schedule 2 and 3 drugs.

i. The prescribers will be identified via the DEA Registration Database; this database will be reviewed on an annual basis and the Dear DEA-Registered Prescriber Letter sent to all new DEA registrants with prescribing authority for drug products subject to this REMS.

ii. NDA/ANDA holders will distribute the letter to each prescriber identified, as described in B.1.c. and B.1.c.i above, a minimum of one time. A copy of the PCD will be enclosed with the letters. In addition, a PCD Order Form will also be included to facilitate the ordering of additional PCDs.

iii. NDA/ANDA holders will make the letter available on the ER/LA Opioid REMS website (www.ER-LA-opioidREMS.com) at the date of the first mailing and will maintain the letters on the website for a time period of one year from the date of the first mailing.

d. NDA/ANDA holders will ensure that within 30 calendar days of the availability of the first prescriber training, as described in B.1.a above, the Dear Professional Associations /Licensing Boards Letter will be sent to the leadership of selected organizations, and professional associations, and request that they disseminate this information to their members.

   i. NDA/ANDA holders will distribute the letter to each organization listed in B.1.d.ii below a minimum of one time. The PCD will be enclosed with the letters.

   ii. The letter and enclosures referenced above, will be sent to the following entities:

      a) State Licensing Boards of:

         1) Medicine (allopathic and osteopathic)
         2) Nursing
         3) Dentistry

      b) Associations of State Licensing Boards:

         1) Federation of State Medical Boards
         2) National Council of State Boards of Nursing
         3) American Association of Dental Boards

      c) Learned Societies and Professional Associations, including, but not limited to:

         1) American Academy of Addiction Psychiatry
         2) American Academy of Family Physicians
         3) American Academy of Hospice and Palliative Medicine
         4) American Academy of Neurology
         5) American Academy of Nurse Practitioners
         6) American Academy of Nursing
         7) American Academy of Orofacial Pain
         8) American Academy of Pain Management
         9) American Academy of Pain Medicine
         10) American Academy of Physical Medicine and Rehabilitation
         11) American Academy of Physician Assistants
         12) American Association of Colleges of Osteopathic Medicine
         13) American Association of Colleges of Nursing

14) American Association of Poison Control Centers
15) American Board of Medical Specialties
16) American Board of Orofacial Pain
17) American College of Nurse Practitioners
18) American College of Osteopathic Family Physicians
19) American College of Physicians
20) American College of Rheumatology
21) American Dental Association
22) American Dental Education Association
23) American Medical Association
24) American Medical Directors Association
25) American Nurses Association
26) American Nurses Credentialing Center
27) American Osteopathic Association
28) American Osteopathic Association of Addiction Medicine
29) American Pain Society
30) American Society of Addiction Medicine
31) American Society for Pain Management Nursing
32) American Society of Anesthesiologists
33) American Society of Pain Educators
34) Association of American Medical Colleges
35) Council of Medical Specialty Societies
36) Hospice and Palliative Nurses Association
37) National Association of Managed Care Physicians
38) National Association of State Controlled Substances Authorities
39) National Commission on Certification of Physician Assistants
40) National Hospice and Palliative Care Organization

d) Health Professional Continuing Education Accrediting Bodies, including, but not limited to:

1) Alliance for Continuing Medical Education

e. NDA/ANDA holders will ensure that within 30 calendar days of the approval of the REMS, the ER/LA Opioid REMS website (www.ER-LA-opioidREMS.com) will be accessible.

   i. Within 30 days of approval of the REMS, the NDA/ANDA holders will provide electronic access to the PCD via the ER/LA Opioid REMS website.

   ii. The Dear Healthcare Professional Letter and Dear Professional Associations/Licensing Boards Letter will be posted to the website within 30 days of the first CE prescriber training availability.

   iii. An electronic link to FDA's Blueprint posted on the Agency's website will also be displayed.

   NDA/ANDA holders will establish one main toll-free number to answer general questions about the ER/LA opioid REMS and REMS materials as listed in section f below. Product-specific questions or concerns will be routed to the appropriate NDA/ANDA holder.

f. The following materials are part of the ER/LA opioid REMS and are appended:

   - Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids
   - PCD Order Form
   - Dear Healthcare Professional Letter
   - Dear Professional Associations/Licensing Boards Letter
   - ER/LA Opioid REMS website (www.ER-LA-opioidREMS.com)

C. Timetable for Submission of Assessments

NDA/ANDA holders will submit REMS Assessments to the FDA at 6 months and 12 months from the date of REMS approval, and annually thereafter. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. NDA/ANDA holders will submit each assessment so that it will be received by the FDA on or before the due date.

Appendix 1. Medication Guide

Medication Guide *DRAFT*
Zohydro™ (zoh-hye-droh) (hydrocodone bitartrate) CII
Extended-Release Capsules
(10 mg, 15 mg, 20 mg, 30 mg, 40 mg and 50 mg)

This Medication Guide has been approved by the U.S. FDA
Issue: DATE

What is the most important information I should know about Zohydro?

- Zohydro can cause trouble breathing if used incorrectly. The breathing problems can even lead to death. Follow your healthcare provider's directions exactly.
- **Zohydro capsules must be swallowed whole and should never be crushed, chewed or dissolved.** Chewing, crushing or dissolving Zohydro capsules could cause death from overdose.
- **Do not consume alcohol while taking Zohydro.** Even other medicines that may or may not require a prescription, such as cough medicines, can have alcohol in them. Alcohol can increase the risk of overdose and may lead to death.

What is Zohydro?

- Zohydro is a prescription medicine that contains the opioid (narcotic) pain medicine hydrocodone. It is used to treat moderate to severe pain.
- Zohydro is for patients who have constant pain that is expected to last for a long time. It is not for pain that occurs only once in a while.
- **Zohydro is a federally controlled substance (CII).** This is because it contains a strong opioid medicine that some people may abuse. **Selling or giving away Zohydro is against the law.**

Who should not take Zohydro?

Do not take Zohydro if you:

- are having an asthma attack or have severe asthma, trouble breathing, or other lung problems.
- have a bowel blockage or obstruction (paralytic ileus)

- **What should I tell my healthcare provider before taking Zohydro?**
- **Tell your healthcare provider if you have a history of:**
- trouble breathing or any lung problems
- liver disease
- low blood pressure
- head injury or brain problems
- severe kidney disease
- seizures
- symptoms of constipation or blocked bowels
- thyroid problems
- a disease that affects your gallbladder or pancreas such as pancreatitis
- a condition that affects your adrenal gland, such as Addison's disease
- an enlarged prostate or problems urinating
- abuse of medications or street drugs, alcohol addiction, or mental health problems. Your chance of being addicted to Zohydro is increased.

Tell your healthcare provider if you:

- **are pregnant or planning to become pregnant.**
- **are breastfeeding.** Some hydrocodone passes into breast milk and may harm your baby.
- are taking prescription, over the counter medicines, vitamins or herbal supplements.
- are taking medicines that treat infections or depression.

Be especially careful about taking other medicines that make you sleepy such as:

- other pain medicines
- sleeping pills
- medicines for anxiety
- tranquilizers
- antihistamines
- medicines for nausea
- antidepressants
- muscle relaxants

Do not start taking any medicines while using Zohydro without talking to your healthcare provider first.

How should I take Zohydro?

- Do not change your dose. Take Zohydro exactly as prescribed by your healthcare provider.
- **Zohydro capsules must be swallowed whole and should never be crushed, chewed or dissolved.** Taking chewed, crushed or dissolved Zohydro capsules is very dangerous. You could die from an overdose of the medicine.
- Your healthcare provider may change your dose depending on your reactions to the medicine. Do not change your dose unless your healthcare provider tells you to change it. Do not take Zohydro more often than prescribed.
- Talk with your healthcare provider regularly about your pain. Your healthcare provider can decide if you still need Zohydro, or if you need a different dose.
- **Do not stop taking Zohydro without talking to your healthcare provider**. If you stop taking Zohydro suddenly, you may have withdrawal symptoms such as: nausea, vomiting, stomach cramping, chills, sweating, anxiety, muscle pain.

How do I dispose of unused Zohydro?

- After you stop taking Zohydro, flush unused product down the toilet, unless otherwise directed.

What should I avoid while taking Zohydro?

- **Do not drink alcohol or use prescription or over the counter medicines that contain alcohol.** Using alcohol while taking Zohydro can increase your risk of having an overdose and may lead to death.
- **Do not drive or operate heavy machinery**, until you know how Zohydro affects you. Zohydro can make you sleepy, dizzy, or lightheaded.

What are the possible side effects of Zohydro?

The most common side effects of Zohydro include:

- constipation
- nausea
- vomiting
- light-headedness
- dizziness
- headache
- drowsiness or sleepiness

Call your healthcare provider if you have any of the symptoms listed below:

- severe dizziness
- severe constipation
- severe vomiting
- abdominal pain, or abdominal bloating

Get emergency medical help if you have:

- trouble breathing or shortness of breath
- extreme drowsiness, feel faint, confused
- abnormal heart beat problems
- **allergic reactions** such as: trouble breathing, pounding heart beat, chest pain, swelling of the face tongue or throat

These are not all the possible side effects of Zohydro. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088**.**

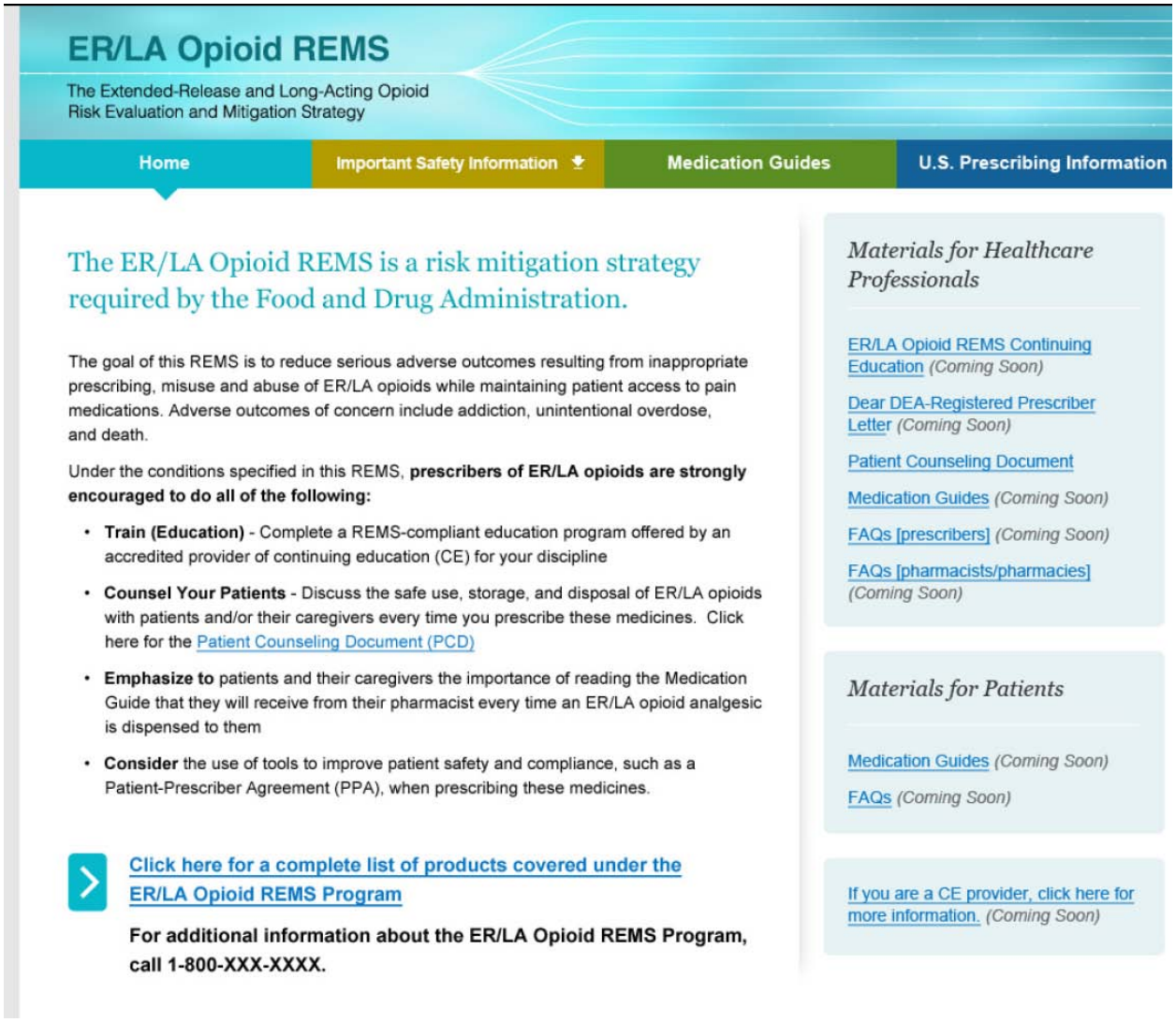
For more information go to www.FDA.gov

For more information about Zohydro go to zohydrorems.com or call 1-866-ZOGENIX.

Manufactured by: Alkermes Gainesville LLC, Gainesville, GA.

Manufactured for: Zogenix, Inc., San Diego, CA

Appendix 2. Screenshots of Opioid REMS Website



Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions that are indicated for use as analgesics.

These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal buprenorphine, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

ER/LA opioid analgesics can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ER/LA opioid analgesics in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. **ER/LA opioid analgesics are not indicated for acute pain. Additionally, ER hydromorphone and transdermal fentanyl products are indicated for use in opioid-tolerant patients only. For some of the other ER/LA opioid analgesics, certain dosage strengths or certain doses are for use in opioid-tolerant patients only.** Consult the individual Full Prescribing Information for dosing instructions for patients who are not opioid tolerant. ER/LA opioid analgesics are not intended for acute pain, pain that is mild or not expected to persist for an extended period of time, or for use on an as-needed basis.

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ER/LA opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms leads to rapid release and absorption of a potentially fatal dose of the opioid agonist. For patients who have difficulty swallowing their medication whole, certain oral products may be opened and sprinkled on applesauce – refer to the product-specific Full Prescribing Information.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated since this may cause choking or overdose resulting in death. Avoid direct external heat sources to transdermal application site and surrounding area.

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. Additionally, ER hydromorphone and transdermal fentanyl products are contraindicated for use in opioid non-tolerant patients. **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

Serious adverse reactions of ER/LA opioid analgesics include life threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

Accidental exposure of ER/LA opioids, especially in children, can result in death.

With methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. A positive-controlled study of the effects of transdermal buprenorphine on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a transdermal buprenorphine dose of 10 mcg/hour; however, a transdermal buprenorphine dose of 40 mcg/hour (given as two 20 mcg/hour transdermal buprenorphine systems) was observed to prolong the QTc interval.

The most common adverse reactions of ER/LA opioid analgesics include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Additionally, the following have been reported with transdermal buprenorphine and fentanyl products: application site pruritus, application site erythema, and application site rash. Refer to the individual Full Prescribing Information for all product-specific adverse reactions.

Adverse Event Reporting

Please report all suspected adverse reactions associated with the use of the specific ER/LA opioid analgesic to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm *or*
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf.

Patient Counseling Document and Medication Guide

The Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is a tool unique to this REMS designed to facilitate important discussions with your patients for whom you select an ER/LA opioid analgesic. The PCD should be provided to the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely.

Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as you prescribe them, the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics.

It is important that you encourage your patients to read the relevant Medication Guide when they pick up their prescription from the pharmacy. The Medication Guide provides important information on the safe and effective use of the specific ER/LA opioid analgesic prescribed.

ER/LA Opioid REMS

The Extended-Release and Long-Acting Opioid Risk Evaluation and Mitigation Strategy

Home | Important Safety Information | Medication Guides | U.S. Prescribing Information

Products covered under the ER/LA Opioid REMS Program, with Prescribing Information & Medication Guides

Brand Name Products

Trade Name	Generic Name	Sponsor	Links
Avinza®	Morphine Sulfate Extended-release Capsules	Pfizer	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Butrans®	Buprenorphine Transdermal System	Purdue Pharma L.P.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Dolophine®	Methadone Hydrochloride Tablets	Roxane Laboratories, Inc.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Duragesic®	Fentanyl Transdermal System	Janssen Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
***Embeda®**	Morphine Sulfate and Naltrexone Extended-release Capsules	Pfizer	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Exalgo®	Hydromorphone Hydrochloride Extended-release Tablets	Mallinckrodt	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Kadian®	Morphine Sulfate Extended-release Capsules	Actavis	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
MS Contin®	Morphine Sulfate Controlled-release Tablets	Purdue Pharma L.P.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Nucynta® ER	Tapentadol	Janssen Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Opana® ER	Oxymorphone Hydrochloride Extended-release Tablets	Endo Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
OxyContin®	Oxycodone Hydrochloride Controlled-release Tablets	Purdue Pharma L.P.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
***Palladone®**	Hydromorphone Hydrochloride Extended-release Capsules	Purdue Pharma L.P.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*

*No longer being marketed, but is still approved.

***Not currently being marketed, but is still approved.

Generic Products

Drug Name	Generic Name	Sponsor	Links
Fentanyl	Fentanyl Extended-release Transdermal System	Actavis	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Fentanyl	Fentanyl Extended-release Transdermal System	Mallinckrodt	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Fentanyl	Fentanyl Extended-release Transdermal System	Mylan Technologies, Inc.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Fentanyl	Fentanyl Extended-release Transdermal System	Noven, Inc.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Fentanyl	Fentanyl Extended-release Transdermal System	Teva Pharmaceuticals USA	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Fentanyl	Fentanyl Extended-release Transdermal System	Watson Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone HCl Tablets	ThePharmaNetwork	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone HCl Tablets	Mallinckrodt	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone HCl Tablets	Sandoz	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone HCl Oral Solution	Roxane Laboratories, Inc.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone Hydrochloride Intensol™ Oral Concentrate	Roxane Laboratories, Inc.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone Hydrochloride Tablets	Roxane Laboratories, Inc.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Methadone Hydrochloride	Methadone HCl Oral Solution	VistaPharm	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Morphine Sulfate	Morphine Sulfate Extended-release Tablets	Endo Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Morphine Sulfate	Morphine Sulfate Extended-release Tablets	Nesher Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Morphine Sulfate	Morphine Sulfate Extended-release Tablets	Mallinckrodt	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Morphine Sulfate	Morphine Sulfate Extended-release Capsules	Watson Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Morphine Sulfate	Morphine Sulfate Extended-release Tablets	Rhodes Pharmaceuticals L.P.	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Oxycodone Hydrochloride	**Oxycodone HCl Extended-release Tablets	Mallinckrodt	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Oxycodone Hydrochloride	**Oxycodone HCl Extended-release Tablets	Teva Pharmaceuticals USA	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Oxycodone Hydrochloride	**Oxycodone HCl Extended-release Tablets	Endo Pharmaceuticals	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*
Oxymorphone Hydrochloride	Oxymorphone HCl Extended-release Tablets	Actavis	• U.S. Prescribing Information *(Coming Soon)* • Medication Guide *(Coming Soon)*

** Tentatively approved products

Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions that are indicated for use as analgesics.

These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal buprenorphine, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

ER/LA opioid analgesics can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ER/LA opioid analgesics in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. **ER/LA opioid analgesics are not indicated for acute pain. Additionally, ER hydromorphone and transdermal fentanyl products are indicated for use in opioid-tolerant patients only. For some of the other ER/LA opioid analgesics, certain dosage strengths or certain doses are for use in opioid-tolerant patients only.** Consult the individual Full Prescribing Information for dosing instructions for patients who are not opioid tolerant. ER/LA opioid analgesics are not intended for acute pain, pain that is mild or not expected to persist for an extended period of time, or for use on an as-needed basis.

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ER/LA opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms leads to rapid release and absorption of a potentially fatal dose of the opioid agonist. For patients who have difficulty swallowing their medication whole, certain oral products may be opened and sprinkled on applesauce – refer to the product-specific Full Prescribing Information.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated since this may cause choking or overdose resulting in death. Avoid direct external heat sources to transdermal application site and surrounding area.

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. Additionally, ER hydromorphone and transdermal fentanyl products are contraindicated for use in opioid non-tolerant patients. **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

Serious adverse reactions of ER/LA opioid analgesics include life threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

Accidental exposure of ER/LA opioids, especially in children, can result in death.

With methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. A positive-controlled study of the effects of transdermal buprenorphine on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a transdermal buprenorphine dose of 10 mcg/hour; however, a transdermal buprenorphine dose of 40 mcg/hour (given as two 20 mcg/hour transdermal buprenorphine systems) was observed to prolong the QTc interval.

The most common adverse reactions of ER/LA opioid analgesics include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Additionally, the following have been reported with transdermal buprenorphine and fentanyl products: application site pruritus, application site erythema, and application site rash. Refer to the individual Full Prescribing Information for all product-specific adverse reactions.

Adverse Event Reporting

Please report all suspected adverse reactions associated with the use of the specific ER/LA opioid analgesic to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm *or*
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf.

Patient Counseling Document and Medication Guide

The Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids is a tool unique to this REMS designed to facilitate important discussions with your patients for whom you select an ER/LA opioid analgesic. The PCD should be provided to the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely.

Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as you prescribe them, the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics.

It is important that you encourage your patients to read the relevant Medication Guide when they pick up their prescription from the pharmacy. The Medication Guide provides important information on the safe and effective use of the specific ER/LA opioid analgesic prescribed.

Selected Important Safety Information

ABUSE POTENTIAL AND RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral dosage forms containing
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions that are indicated for use as analgesics.

These drug products will be collectively referred to as Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics.

ER/LA prescription opioid analgesics are opioid agonists and Schedule II or, Schedule III, as is the case with transdermal buprenorphine, controlled substances with abuse liabilities similar to other opioid agonists. Schedule II and Schedule III opioid substances have high potential for abuse and risk of fatal overdose due to respiratory depression.

ER/LA opioid analgesics can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing ER/LA opioid analgesics in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). Patients should be assessed for their clinical risks for opioid abuse or addiction prior to being prescribed opioids. All patients receiving opioids should be routinely monitored for signs of misuse, abuse and addiction.

ER/LA opioid analgesics containing buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. **ER/LA opioid analgesics are not indicated for acute pain. Additionally, ER hydromorphone and transdermal fentanyl products are indicated for use in opioid-tolerant patients only. For some of the other ER/LA opioid analgesics, certain dosage strengths or certain doses are for use in opioid-tolerant patients only.** Consult the individual Full Prescribing Information for dosing instructions for patients who are not opioid tolerant. ER/LA opioid analgesics are not intended for acute pain, pain that is mild or not expected to persist for an extended period of time, or for use on an as-needed basis.

Patients considered opioid tolerant are those who are taking at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

ER/LA opioid analgesic formulations have product specific dosage and administration instructions. Refer to the individual Full Prescribing Information for specific doses and dosing recommendations.

ER/LA oral dosage forms must be swallowed whole and must not be cut, broken, chewed, crushed, or dissolved. Taking cut, broken, chewed, crushed or dissolved oral dosage forms leads to rapid release and absorption of a potentially fatal dose of the opioid agonist. For patients who have difficulty swallowing their medication whole, certain oral products may be opened and sprinkled on applesauce – refer to the product-specific Full Prescribing Information.

Transdermal dosage forms must not be cut, damaged, chewed, swallowed or used in ways other than indicated since this may cause choking or overdose resulting in death. Avoid direct external heat sources to transdermal application site and surrounding area.

ER/LA opioid analgesics are contraindicated in patients with a known hypersensitivity to any of the components of ER/LA opioid analgesics, including the respective active ingredients, or in any situation where opioids are contraindicated; in patients who have significant respiratory depression; in patients who have acute or severe bronchial asthma; or in patients who have or are suspected of having paralytic ileus. Additionally, ER hydromorphone and transdermal fentanyl products are contraindicated for use in opioid non-tolerant patients. **These contraindications are not all-inclusive of those for each individual ER/LA opioid analgesic;** therefore, the Full Prescribing Information for the individual ER/LA opioid analgesics must be consulted.

The concomitant use of ER/LA opioid analgesics containing buprenorphine, fentanyl, methadone, or oxycodone with cytochrome P450 3A4 inhibitors may result in increased opioid plasma concentrations and may cause potentially fatal respiratory depression.

Adverse Reactions

Serious adverse reactions of ER/LA opioid analgesics include life threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death.

Accidental exposure of ER/LA opioids, especially in children, can result in death.

With methadone, cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment. Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction. A positive-controlled study of the effects of transdermal buprenorphine on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a transdermal buprenorphine dose of 10 mcg/hour; however, a transdermal buprenorphine dose of 40 mcg/hour (given as two 20 mcg/hour transdermal buprenorphine systems) was observed to prolong the QTc interval.

The most common adverse reactions of ER/LA opioid analgesics include constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, asthenia, and sweating. Additionally, the following have been reported with transdermal buprenorphine and fentanyl products: application site pruritus, application site erythema, and application site rash. Refer to the individual Full Prescribing Information for all product-specific adverse reactions.

Adverse Event Reporting

Please report all suspected adverse reactions associated with the use of the specific ER/LA opioid analgesic to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

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- by mail using the fillable portable document format (PDF) Form FDA 3500, available at http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf.

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Patients and their caregivers should be counseled on: the importance of taking these medicines exactly as you prescribe them, the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics.

It is important that you encourage your patients to read the relevant Medication Guide when they pick up their prescription from the pharmacy. The Medication Guide provides important information on the safe and effective use of the specific ER/LA opioid analgesic prescribed.

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5. DISCLAIMER OF WARRANTIES

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By submitting any unsolicited information and materials, including comments, ideas, questions, designs, and other similar communications (collectively, "Unsolicited Information") to RPC through the Site, you agree to be bound by the following terms and conditions. If you do not agree with these terms and conditions, you should not provide any Unsolicited Information through the Site. All Unsolicited Information will be considered NON-CONFIDENTIAL and NON-PROPRIETARY. RPC may use such communication or material for any purpose whatsoever, including, but not limited to, reproduction, disclosure, transmission, publication, broadcast, and further posting. Further, RPC is free to use any ideas, concepts, know-how, or techniques contained in any communication or material you send to the site for any purpose whatsoever, including, but not limited to, developing, manufacturing, and marketing products. By submitting any Unsolicited Information, you are granting us a perpetual, royalty-free and irrevocable right and license to use, reproduce, modify, adapt, publish, translate, distribute, transmit, publicly display, publicly perform, sublicense, create derivative works from, transfer and sell such Unsolicited Information and to use your name and other identifying information in connection with such Unsolicited Information.

Under no circumstances, should you use this Site or any of the fax and mailing addresses on the Site to send RPC confidential or proprietary information. RPC does not want to receive such confidential or proprietary information.

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Links Out — This Site may provide links or references to other Web sites not affiliated with RPC. RPC has not reviewed the content of Web sites that may be linked to its Site, makes no representations about the content of the Web sites, and is not responsible for the content of any other Web site linked to this Site. Linking to any pages off this Site is at your own risk. RPC shall not be liable for any damages or injury arising from users' access to such Web sites.

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ACTUAL OR ATTEMPTED UNAUTHORIZED USE OF THE SITE MAY RESULT IN CRIMINAL AND/OR CIVIL PROSECUTION. RPC RESERVES THE RIGHT TO VIEW, MONITOR, AND RECORD ACTIVITY ON THE SITE WITHOUT NOTICE OR PERMISSION FROM YOU. ANY INFORMATION OBTAINED BY MONITORING, REVIEWING, OR RECORDING IS SUBJECT TO REVIEW BY LAW ENFORCEMENT ORGANIZATIONS IN CONNECTION WITH INVESTIGATION OR PROSECUTION OF POSSIBLE ILLEGAL ACTIVITY ON THE SITE. RPC WILL ALSO COMPLY WITH ALL COURT ORDERS AS WELL AS ALL LAW ENFORCEMENT AND REGULATORY INQUIRIES INVOLVING REQUESTS FOR SUCH INFORMATION.

PRIVACY POLICY

The privacy of Site users' personal information is important to RPC. This Privacy Policy describes information that may be collected about Site users; how Site user information is used; how RPC protects it; and what choices Site users have on how that information is used.

1. This privacy policy covers the following types of information:
   This Privacy Policy covers RPC's treatment of any personally identifiable information that RPC collects when you are on this Website. This Privacy Policy does not apply to the practices of companies that RPC does not own or control, or to people that RPC does not employ or manage. Information collection and use will be handled in the following manner set forth in this Privacy Policy.
2. PERSONAL INFORMATION WE COLLECT.
   Information we collect from visitors:
   Visitors to RPC Sites can access the Site's home page, and browse some areas of the Site, without disclosing any personally identifiable information. We do track information provided to us by your browser, including the Web site you came from (known as the referring URL), the type of browser you use, the time and date of access, and other information that does not personally identify you. In addition, we gather information about you that is automatically collected by our Web server, such as your IP address and domain name. RPC may use Web server and browser information to individually customize its offerings and presentations if you submit your personal information
3. RPC will take steps to safeguard any information you share with us. By providing any personal information, you acknowledge and agree that, despite efforts to safeguard such personal information, no system, including the RPC systems, are perfect and no data is completely safe from inadvertent, unintended or unauthorized disclosure. RPC stores the information you provide about yourself in a database in order to provide you with the information you request. The information is stored for the lifetime of the database unless you request that it be removed.
4. The information on this website is intended for individuals 18 years of age or older. We do not knowingly collect personally identifiable data from Site visitors under the age of 18.
5. Except as described above, RPC will not intentionally otherwise use or disclose any of your personally identifiable information , except to the extent reasonably necessary: (i) to correct technical problems and malfunctions, to technically process your information and to determine the effectiveness of our projects; (ii) to protect the security and integrity of our website; (iii) to protect our rights and property and the rights and property of others; (iv) to take precautions against liability; (v) to the extent required by law or to respond to judicial process; or (vi) to the enforcement agencies or for an investigation on a matter related to public safety, as applicable.
6. Cookies, log files, and pixel-tags (Web beacons) are technologies used by the RPC Sites to identify a user as the user moves through RPC Sites. Your browser allows us to place some information (session based IDs and/or persistent cookies) on your computer's hard drive that identifies the computer you are using. We may use cookies to personalize our Web sites and to track your usage across other RPC Sites. Your Web browser can be set to allow you to control whether you will accept cookies, reject cookies, or to notify you each time a cookie is sent to you. If your browser is set to reject cookies, Web sites that are cookie-enabled will not recognize you when you return to the Web site, and some Web site functionality may be lost. The Help section of your browser will tell you how to prevent your browser from accepting cookies. On occasion, we contract with third parties to place cookies on your computer's hard drive. Although cookies do not normally contain personally identifiable information, if you have provided us information about you, we may associate your registration information with cookies or other tracking utilities our Web site places on your computer's hard drive. Associating a cookie with your registration data allows us to offer increased personalization and functionality. Without cookies, this functionality would not be possible.
7. As a resource to Site visitors, RPC may provide links to other websites. Site users should carefully review the privacy policies and practices of these websites, as RPC cannot control or be responsible for the privacy practices of other Web sites.
8. THIRD PARTIES. RPC may share some kinds of information with third parties as described below:
   - **Companies and people who work for RPC:** RPC contracts with other companies and individuals to help RPC administer the Opioid REMS Program. If you are a health care professional, RPC may validate your licensure status and other information against available databases that list licensed health care professionals. In order to perform their jobs, these other companies may have limited access to some of the personal information RPC maintain about our users. Other companies may collect information on our behalf through their sites. This occasionally incorporates the use of frames on the site that will not show the URL you are visiting in the browser address window. We require such companies to comply with the terms of our privacy policies, to limit their access to any personal information to the minimum necessary to perform their obligations, and not to use the information they may access for purposes other than fulfilling their responsibilities to us. We use our best efforts to limit other companies' use of personally identifiable or health care information.
   - **Legal requirements:** We may release account and other personal information when RPC believes that its release is required to comply with the law regulations, rules or local ordinances. We may release personal health information if, in our judgment after review by an attorney, the release is compelled by law or regulation, or if the release may be necessary to prevent the death or serious injury of an individual.

By using this Site and the contents and services available to you on our Website, you consent to our collection and use of your information as described above. RPC will continuously assess its practices to ensure that your privacy is respected. RPC may amend this Privacy Policy from time to time. If RPC makes any substantial changes in the way RPC uses your personal information RPC will notify you by posting a prominent announcement on RPC's Website.

See also RPC's Terms of Use for additional information.

Patient Counseling Document on Extended-Release / Long-Acting Opioids
Patient Name:
The DOs and DON'Ts of Extended-Release / Long - Acting Opioids
DO: • Read the **Medication Guide** • Take your medicine exactly as prescribed • Store your medicine away from children and in a safe place • Flush unused medicine down the toilet • Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
Call 911 or your local emergency service right away if: • You take too much medicine • You have trouble breathing, or shortness of breath • A child has taken this medicine
Talk to your healthcare provider: • If the dose you are taking does not control your pain • About any side effects you may be having • About all the medicines you take including over-the-counter medicines, vitamins, and dietary supplements
DON'T: • **Do not** give your medicine to others • **Do not** take medicine unless it was prescribed for you • **Do not** stop taking your medicine without talking to your healthcare provider • **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider. • **Do not** drink alcohol while taking this medicine
For additional information on your medicine go to: **dailymed.nlm.nih.gov**

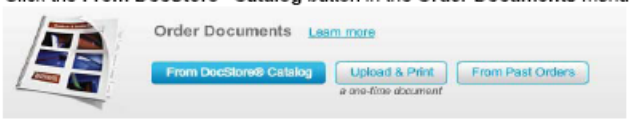
Patient Counseling Document on Extended-Release / Long-Acting Opioids
Patient Name:
Patient Specific Information
Take this card with you every time you see your healthcare provider and tell him/her: • Your complete medical and family history, including any history of substance abuse or mental illness • The cause, severity, and nature of your pain • Your treatment goals • All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements • Any side effects you may be having **Take your opioid pain medicine exactly as prescribed by your healthcare provider.**

HOW TO ORDER

Extended-Release/Long-Acting Opioids
Patient Counseling Document (PCD) Order Form

OPTION 1

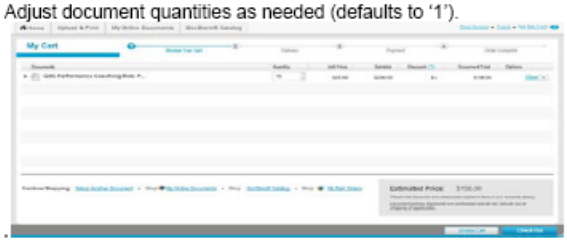
1. Order on line by visiting - https:docstore.fedex.com/patientcouncilingdoc
2. Click the **From DocStore® Catalog** button in the **Order Documents** menu to start your order.



3. Select document "Patient Counseling Document" to order and click **Add to cart**
4. **My Cart** will display momentarily at the top right of your screen as you add documents. **Continue to Checkout** (Please note there is no cost for the Patient Counseling Documents).

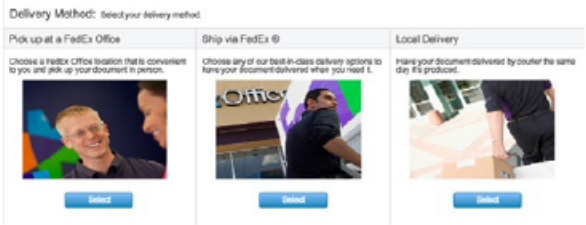
My Cart

Adjust document quantities as needed (defaults to '1').



Shipping and Production Details

1. Click an option in the Delivery Method list to specify if you would like to pick up your order (Please note there is no cost for shipping).



Contact and Recipient Information

1. Complete the **Contact Info** and **Recipient** forms.
2. Click **Submit Order** to complete your order

OPTION 2: **FAX your order by using the order form on the back of this document**

FAX ORDER FORM

Extended-Release/Long-Acting Opioids Patient Counseling Document (PCD) Order Form	
Patient Counseling Document **Tear-Off Sheets (25 sheets per pad)**	
FAX ORDER FORM 1 – Complete all information below 2 – Fax your order to: (917) 777-0357 3 – You will receive an order confirmation	
There is no cost for the documents or for shipping.	
Date:	
Ship to:	
Number of packs of 25 Requested:	
Name:	
Institution or Practice:	
Department:	
Street Address:	
City:	
State:	
ZIP:	
Telephone Number (w/area code):	
Email address:	
Delivery Options – Please circle your choice.	**1- Pick up at local FedEx Office location** **2- Ship via FedEx** **3- Local delivery**
Questions? Please call (917) 229-2418	

Appendix 3. Dear Registered DEA-Prescriber Letter

08 March 2012

Dear Healthcare Professional Letter

Important Drug Warning

Subject:	**Announcement of the creation of a single, shared REMS (Risk Evaluation and Mitigation Strategy) program for all Extended-Release/Long-Acting Opioid Analgesic Products for which there is a potential risk of misuse, abuse, addiction, or overdose. The Food and Drug Administration (FDA) has required all manufacturers of ER/LA opioids to participate in this program.**

[Date]

Dear **DEA**-Registered Prescriber:

Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics have been an important option for the management of chronic pain in the U.S. and can be safe and effective in appropriately selected patients when used as directed. However, serious adverse outcomes may occur in patients at risk for abuse or misuse, as well as with accidental or intentional improper use.

Opioid analgesics are associated with serious risks and are at the center of a major public health crisis of addiction, misuse, abuse, overdose, and death. The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh their risks.

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while maintaining access to analgesic medications for legitimate medical purposes. Adverse outcomes of concern include addiction, unintentional overdose, and death.

Under the conditions specified in this REMS, **you are strongly encouraged to do all of the following:**

- **Train (Education) -** Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) for your discipline
- **Counsel Your Patients -** Discuss the safe use, storage, and disposal of ER/LA opioids with patients and/or their caregivers every time you prescribe these medicines. The attached *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids* can be used to facilitate these discussions with patients and/or their caregivers every time you prescribe an ER/LA opioid analgesic
- **Emphasize to** patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them
- **Consider** the use of tools to improve patient safety and compliance, such as a Patient-Prescriber Agreement (PPA), when prescribing these medicines.

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral-dosage forms containing
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions that are indicated for use as analgesics.

REMS-compliant Training (Education) Programs

ER/LA opioid analgesics should be prescribed in accordance with the REMS-compliant education programs. The central component of the ER/LA Opioid Analgesics REMS program is safety education for prescribers and patients.

Education for prescribers will include general and product-specific drug information, including information on weighing the benefits and risks of opioid therapy, choosing patients appropriately, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, and addiction.

At www.ER-LA-opioidREMS.com, you will also find resources that will assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic, including a tool unique to this REMS designed to facilitate these discussions – the *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids*. The PCD should be provided to the patient and/or their caregiver at the time of prescribing. It contains important safety information about the drug products subject to this REMS and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely. The site can also direct you to those REMS-compliant continuing education courses offered by accredited CE providers who have requested listing.

Patients and their caregivers should be counseled on:

- the importance of taking these medicines exactly as you prescribe them,
- the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household acquaintances to avoid risks from unintended exposure,
- the importance of not sharing these medications, even if someone has the same symptoms as the patient, *and*
- the proper methods of disposal of unneeded ER/LA opioid analgesics.

Adverse Event Reporting

In order to keep effective medical products available on the market, the FDA relies, in part, on the voluntary reporting of adverse events. The FDA uses these reports to monitor the safety of drug products after they are approved for use. Your report may be the critical piece of information that prompts a modification in use or design of a drug product, improves its safety profile, and leads to increased patient safety.

Please report all suspected adverse reactions associated with the use of the covered ER/LA opioid analgesics to the appropriate company. You may also report adverse events directly to the FDA's MedWatch Reporting System:

- by calling 1-800-FDA-1088 (1-800-332-1088),

- online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm , *or*
- by mail using the fillable portable document format (PDF) Form FDA 3500, available at http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf .

Information on this REMS and the availability of accredited CE programs on the ER/LA Opioid Analgesic REMS is available online at www.ER-LA-opioidREMS.com.

More information about this REMS can be obtained at:
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

Sincerely,

ER/LA Opioid Analgesic REMS NDA/ANDA Holders

Appendix 4. Dear Professional Associations/Licensing Board Letter

Dear Professional Associations/Licensing Boards Letter

Important Drug Warning

Subject:	**Announcement of the creation of a single, shared REMS (Risk Evaluation and Mitigation Strategy) program for all Extended-Release/Long-Acting Opioid Analgesic Products for which there is a potential risk of misuse, abuse, addiction, or overdose. The Food and Drug Administration (FDA) has required all manufacturers of ER/LA opioids to participate in this program.**

[Date]

Dear **<Professional Associations/Licensing Boards>**:

Extended-Release and Long-Acting (ER/LA) prescription opioid analgesics have been an important option for the management of chronic pain in the U.S. and can be safe and effective in appropriately selected patients when used as directed. However, serious adverse outcomes may occur in patients at risk for abuse or misuse, as well as with accidental or intentional improper use.

Opioid analgesics are associated with serious risks and are at the center of a major public health crisis of addiction, misuse, abuse, overdose, and death. The U.S. Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh their risks.

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while maintaining access to analgesic medications for legitimate medical purposes. Adverse outcomes of concern include addiction, unintentional overdose, and death.

Under the conditions specified in this REMS, **we ask that you strongly encourage your <licensees/members> to do all of the following:**

- **Train (Education) -** Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) for your discipline
- **Counsel Your Patients -** Discuss the safe use, storage, and disposal of ER/LA opioids with patients and/or their caregivers every time you prescribe these medicines. The attached *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids* can be used to facilitate these discussions with patients and/or their caregivers every time you prescribe an ER/LA opioid analgesic
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- the proper methods of disposal of unneeded ER/LA opioid analgesics.

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- by calling 1-800-FDA-1088 (1-800-332-1088),
- online at https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm , *or*

- by mail using the fillable portable document format (PDF) Form FDA 3500, available at http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf .

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More information about this REMS can be obtained at:
http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm .

Sincerely,

ER/LA Opioid Analgesic REMS NDA/ANDA Holders